IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS, EASTERN DIVISION

MELANIE STACEL, Plaintiff, v. TEVA PHARMACEUTICALS USA, INC. Defendant.	Case No. 08-CV-1143 Judge Joan B. Gottschall Magistrate Judge Jeffrey Cole

NOTICE OF SUPPLEMENTAL AUTHORITY IN FURTHER SUPPORT OF DEFENDANT TEVA PHARMACEUTICALS USA, INC.'S MOTION TO DISMISS

Defendant Teva Pharmaceuticals USA, Inc. ("Teva") respectfully submits this Notice of Supplemental Authority to call the Court's attention to recent federal case law and to the recent Final Rule published by the United States Food and Drug Administration ("FDA"), which authority further supports Teva's Motion to Dismiss Plaintiff's Second Amended Complaint.

Teva refers the Court to the decisions of the District Court for the Southern District of Florida in *Bolin v. SmithKline Beecham Corp.*, 2008 WL 3286973 (S.D. Fla., Aug. 7, 2008) (Exhibit A); *Masterson v. SmithKline Beecham Corp.*, 2008 WL 3262690 (S.D. Fla., Aug. 7, 2008) (Exhibit B); and *Valerio v. SmithKline Beecham Corp.*, 2008 WL 3286976 (S.D. Fla., Aug. 7, 2008) (Exhibit C). In each case, plaintiff sought to recover damages for injuries allegedly caused by a generic drug. The district court in each case ratified Teva's position as to federal preemption of products liability claims against a generic drug manufacturer. To arrive at its conclusion, the district court carefully analyzed many of the same decisions that are cited by Teva in its moving and reply papers in support of its Motion to Dismiss in the instant action, including the Third Circuit opinion in *Colacicco v. Apotex, Inc.*, 521 F.3d 253 (3d Cir. 2008),

aff'g, 432 F. Supp. 2d 514 (E.D. Pa. 2006) and the recent decisions in *Mensing v. Wyeth, et al.*, 2008 WL 2444689 (D. Minn. June 18, 2008), and *Gaeta v. Perrigo Pharmaceuticals Co.,* 2008 WL 2548813 (N.D. Cal. June 13, 2008). The district court held, in reliance upon the reasoning in *Mensing*, that plaintiffs' claims were preempted:

> This Court agrees with the analysis and conclusion of the decision in *Mensing* finding preemption of state law failure to warn claims against a generic manufacturer/distributor such as the [generic manufacturer] Defendants. Because the FDA, pursuant to the FDCA statutory scheme as amended by the Hatch Waxman Act, requires generic drugs to have the same labeling as listed drugs, these federal laws preempt such a state law claim. Unlike a manufacturer of a listed drug, a generic manufacturer has a limited ability to even suggest a labeling change, subject solely to the discretion of the FDA to change the labeling for both the generic and the listed drug. Therefore, compliance with a state law duty to warn would conflict with the federal statutory scheme.

Bolin, 2008 WL 3286973 at 7; *Masterson,* 2008 WL 3262690 at 4; 2008 WL 3286976 at 7.

In its Memorandum in Support of its Motion to Dismiss, Teva discussed FDA's January 2008 proposed amendments to its rules governing changes to approved labeling. Teva also now refers the Court to FDA's Final Rule on Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics and Medical Devices, 73 Fed. Reg. 49603, 49605 (August 22, 2008) (Exhibit D), published just two weeks ago, wherein FDA set out express guidelines for label changes through "changes being effected" ("CBE") supplements pursuant to 21 C.F.R. § 314.70(c)(6)(iii). Notably, the Final Rule is directed *exclusively* to New Drug Application holders and, by implication, this is yet further evidence that warning enhancement through CBE supplementation is *not* available to Abbreviated New Drug Application holders. With respect to preemption, FDA rejects arguments that its position is inconsistent with Congressional intent. It also comments in the Preamble to this Final Rule that "the absence of an express preemption provision with respect to drugs [does not affect] the application of implied preemption."

This recent federal case law and FDA's August 22, 2008 Final Rule, together with all the reasons set forth in Teva's moving and reply papers, mandate that Teva's Motion to Dismiss be granted and Plaintiff's Second Amended Complaint be dismissed.

Date: September 9, 2008

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CERTIFICATE OF SERVICE

Ameri R. Giannotti, an attorney, certifies that on September 9, 2008 she electronically filed the foregoing NOTICE OF SUPPLEMENTAL AUTHORITY IN FURTHER SUPPORT OF DEFENDANT TEVA PHARMACEUTICALS USA, INC.'S MOTION TO DISMISS using the ECF system which will automatically send e-mail documentation of such filing to the parties listed below:

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EXHIBIT A

Bolin ex rel. Bolin v. SmithKline Beecham Corp.
S.D.Fla.,2008.
Only the Westlaw citation is currently available.
United States District Court,S.D. Florida.
Haley M. BOLIN, a minor by Jennifer J. BOLIN and Nathan Bolin, and Jennifer J. Bolin and Nathan Bolin. Individually, Plaintiffs,
v.
SMITHKLINE BEECHAM CORPORATION d/b/a Glaxosmithkline, a Pennsylvania corporation, Apotex Corp. and Apotex, Inc., Defendants.
No. 08-60523-CIV.

Aug. 7, 2008.

Bryan Frederick Aylstock, Joshua A. Jones, Aylstock Witkin Kreis & Overholtz PLLC, Pensacola, FL, Jennifer R. Liakos, Karen Barth Menzies, Robinson, Calcagnie & Robinson, Inc., Newport Beach, CA, Kate E. Gillespie, Ronald L.M. Goldman, Baum, Hedlund, Aristel & Goldman, P.C., Los Angeles, CA, for Plaintiffs.
Maria Helena Ruiz, Mercer Kaye Clarke, Clarke Silverglate & Campbell, P.A., Michael Alexandar Garcia, Fowler White Burnett, Miami, FL, for Defendants.

ORDER DENYING MOTION TO REMAND ORDER GRANTING IN PART MOTION TO DISMISS

JAMES I. COHN, District Judge.
***1** THIS CAUSE is before the Court upon Plaintiffs' Motion to Remand and Motion for Attorneys Fees and Costs [DE 15] and Defendants Apotex Corp. and Apotex Inc.'s Motion to Dismiss [DE 6]. The Court has carefully considered the motions, responses and replies thereto, and is otherwise fully advised in the premises.[FN1]

FN1. Plaintiffs did not file a reply in support of their motion to remand.

I. BACKGROUND

Plaintiffs filed this action in Broward County Circuit Court alleging various claims of negligence and product liability against manufacturers and/or distributors of a psychopharmaceutical drug that is alleged to have caused birth defects in the minor child in this case. Plaintiffs are residents and citizens of states other than Pennsylvania and Florida. Defendant Smith klineBeecham Corporation is a citizen of Pennsylvania. Defendant Apotex Corporation ("Apotex Corp.") has its principal place of business in Weston, Florida, and is a wholly owned subsidiary of Defendant Apotex, Inc., a Canadian corporation (collectively, "Apotex Defendants").

On April 11, 2008, prior to being served, Defendant SmithKline Beecham removed this case to this Court. The Florida defendant, Apotex Corp., was not served until April 16, 2008. On April 28, 2008, the Apotex Defendants moved to dismiss this case based upon federal preemption. On May 8, 2008, Plaintiffs moved to remand the case pursuant to 28 U.S.C. § 1441(b), the "forum-state defendant rule" because a Florida defendant, Apotex Corp., is in the case. Defendants oppose the motion to remand

II. MOTION TO REMAND

On a motion to remand, the removing party bears the burden of establishing jurisdiction. *Tapscott v. M.S. Dealer Serv. Corp.*, 77 F.3d 1353, 1356 (11th cir.1996), *overruled on other grounds by Cohen v. Office Depot, Inc.*, 204 F.3d 1069, 1076 (11th Cir.2000); *Diaz v. Sheppard*, 85 F.3d 1502, 1505 (11th Cir.1996). In this case, there is no dispute that complete diversity exists, both now and at the time of removal. However, Plaintiffs seek remand because pursuant to 28 U.S.C. § 1441(b), a forum state defendant cannot remove an action. The statute states that for diversity jurisdiction, any "such action shall be removable only if none of the parties in interest **properly joined and served** as defendants is a citizen of the State in which such action is brought."28 U.S .C. § 1441(b) (emphasis added). Thus, even though a federal court may have original jurisdiction over an action, the forum defendant rule forbids removal of such action.

A. Forum Defendant Rule[FN2]

FN2. This Court previously addressed this issue in *Masterson v. Apotex, et al,* 2008 WL 2047979 (S.D.Fla.2008) (Case No. 07-61665-Civ). The Court repeats most of that decision herein.

Plaintiff states that United States Court of Appeals for the Eleventh Circuit precedent, as well as Supreme Court precedent, mandate remand in this case. However, Plaintiff has incorrectly equated diversity jurisdiction with the forum defendant rule's ban on removal of certain cases that otherwise meet the diversity jurisdiction requirement. *Hurley v. Motor Coach Industries, Inc.,* 222 F.3d 377, 379-380 (7th Cir.2000) (forum defendant rule is not jurisdictional); *Snapper, Inc. v. Redan,* 171 F.3d 1249, 1258 (11th Cir.1999). Thus, Plaintiff's reliance on decisions questioning diversity jurisdiction cases is not determinative of this forum defendant issue.*Florence v. Crescent Resources, LLC,* 484 F.3d 1293, 1297 (11th Cir.2007); *Tillman v. R.J. Reynolds Tobacco,* 253 F.3d 1302, 1305 (11th Cir.2001). Moreover, in this case there is no issue of fraudulent joinder, no non-diverse defendant, and diversity jurisdiction is clearly present.

***2** Where complete diversity exists, it is unclear whether the inclusion of an unserved resident defendant defeats removal under 28 U.S.C. § 1441(b).[FN3] The plain language of the statute requires the resident defendant to be "properly joined and served" to defeat removal. 28 U.S.C. § 1441(b). Thus, the present situation is distinguishable from cases where "the existence of diversity is determined from the fact of citizenship of the parties named and not from the fact of service."*New York Life Ins. Co. v. Deshotel,* 142 F.3d 873, 883 (5th Cir.1998). Rather, in the more specific context of the forum-state defendant rule in § 1441(b), Congress has apparently determined that the Court only look at "properly joined and served" defendants. At least in passing, one Circuit Court of Appeals agrees with this conclusion. *McCall v. Scott,* 239 F.3d 808, 813, n. 2 (6th Cir.2001).

FN3. Where there is no issue of fraudulent joinder of a defendant, the forum defendant rule does not arise often. It can only arise, as in this case, when plaintiffs are not "forum state" citizens.

The district court decisions on this issue are split. Defendants rely upon *Ott v. Consolidated Freightways Corporation,* 213 F.Supp.2d 662, 665 (S.D.Miss.2002), which answers the precise question of this case by concluding that unserved defendants at the time of removal may be ignored for § 1441(b) purposes. Other cited cases following *Ott* are cited as well. *Stan Winston Creatures, Inc. v. Toys "R" Us, Inc.,* 314 F.Supp.2d 177, 180-81 (S.D.N.Y.2003) (case remanded because defendant in question was in fact served, but legal conclusion of *Ott* followed); *Clawson v. FedEx Ground Package System, Inc.,* 451 F.Supp.2d 731, 735-36 (D.Md.2006).

In the only published, non-fraudulent joinder decision cited by Plaintiffs, [FN4] the Court in *Oxendine v. Merck and Co., Inc.,* 236 F.Supp.2d 517, 524-25 (D.Md.2002), held that because the law prior to enactment of § 1441(b) stated that where a non-separable controversy involves a resident defendant, the fact that the resident defendant has not been served with process does not justify removal by the non-resident defendant. However, this Court agrees with the decisions concluding that § 1441(b) as amended limits looking only at "properly joined and served" defendants at the time of removal where diversity jurisdiction is not an issue.

FN4. In its research, the Court uncovered a Circuit Court of Appeals' description of the district court decision under review in *Holmstrom v. Peterson,* 492 F.3d 383, 385 (7th Cir.2007), wherein the lower court recognized that the plain language of the statute required the forum defendant to be properly served to defeat removal, but still held that because there was no indication that plaintiff in that case named the forum state defendant solely to defeat removal, it granted the motion to remand. The Seventh Circuit concluded it lacked jurisdiction to review this procedural defect for other reasons.

Plaintiffs also raise policy concerns regarding acceptance of Defendants' arguments. However, in addition to the statutory language and case law, policy considerations also support Defendants. Removal is "intended to protect out-of-state defendants from possible prejudices in state

court."*Lively v. Wild Oats Markets, Inc.*, 456 F.3d 933, 940 (9th Cir.2006). The purpose of the forum state defendant rule is to allow plaintiffs to choose a forum because a forum state defendant does not need the protection of removal rights. However, in the limited situations such as the present case when a non-forum state defendant removes a case also involving a forum defendant, it is necessary to only consider properly served defendants so as to not allow a plaintiff to thwart removal rights of diverse, non forum state defendants by not serving the forum state defendant.[FN5]To avoid this result, plaintiffs can control the situation by attempting immediate service upon a forum state defendant when filing such a case in state court.

> FN5. Plaintiffs also rely upon a series of unpublished decisions from the Eastern District of Pennsylvania involving some of the same parties as the present case. *Takia Malone v. GlaxoSmithKline PLC,* et al, Case No. 07-5048, Order at docket entry 4 (December 4, 2007). However, in *Malone,* SmithKlineBeecham was both the forum state defendant and the removing defendant. The Court there concluded that allowing removal because SmithKlineBeecham was not yet served would defeat congressional intent, citing to *Oxendine.*This Court not only disagrees with *Oxendine,* but factually distinguishes the Pennsylvania cases because in the present case the removing defendant was not the forum-state defendant.

B. Lack of Complete Consent and Amount in Controversy

***3** Plaintiffs also argue that removal was improper because the Apotex Defendants did not consent to removal and the amount in controversy does not satisfy subject matter jurisdiction. Turning to the amount in controversy, because the plaintiff's state court complaint seeks an unspecified amount of damages, the defendant must establish the amount in controversy by a preponderance of the evidence. *Tapscott,* 77 F.3d 1359-60.Defendants argue that the Complaint's allegations of "immature lung development and severe respiratory problems" in an infant born with "severe respiratory distress," make it more likely than not that the damages will be over $75,000. Complaint, ¶¶ 19, 30. Plaintiffs seek damages for pecuniary loss, loss of consortium, general and medical damages and related expenses, and punitive damages. Complaint, ¶¶ 40-42, 46-48, 58-60, 66-68, 74-76, 85-87. The Court can conclude that these damage allegations alone meet Defendants' burden to show that the amount in controversy is greater than $75,000.

Turning next to Plaintiff's argument regarding lack of unanimity of consent, an exception to the unanimity requirement is lack of service upon the other defendants. *White v. Bombardier Corp.*, 313 F.Supp.2d 1295, 1299-1300 (N.D.Fla.2004), citing *Murphy Bros., Inc. v. Michetti Pipe Stringing, Inc.*, 526 U.S. 344, 354, 119 S.Ct. 1322, 143 L.Ed.2d 448 (1999). However, there is a split in the case law in cases where multiple defendants are served at different times. Some courts follow the "first-served" defendant rule, which requires a later-served defendant to remove or consent to removal within thirty days of service upon the first-served defendant, even if more than thirty days has passed, while others have held that a later-served defendant has thirty days from its receipt of service to remove with consent of the others. *Smith v. The Health Center of Lake City, Inc.*, 252 F.Supp.2d 1336, 1341-1345 (M.D.Fla.2003) (collecting cases).

In a recent published decision, the United States Court of Appeals for the Eleventh Circuit adopted the later-served defendant rule. *Bailey v. Janssen Pharmaceutica, Inc.*, --- F.3d ----, 2008 WL 2894742 (11th Cir. July 29, 2008). The Court held that the first-served defendant rule deprives later-served defendants of their right to remove a case, and imposes the word "first" into the plain language of 28 U.S.C. § 1446(b). The Eleventh Circuit followed the trend of the other Circuit Court of Appeals who have considered the issue.*McKinney v. Board of Trustees of Mayland Cmty. College*, 955 F.2d 924, 926-27 (4th Cir.1992); *Brierly v. Alusuisse Flexible Packaging, Inc.*, 184 F.3d 527, 533 (6th Cir.1999); *Marano Enterprises of Kansas v. Z-Teca Restaurants, L.P.*, 254 F.3d 753, 755-56 (8th Cir.2001).

Applying the later-served defendant rule to this case requires one more step. Here, the case was removed even before service. However, using the reasoning of the later-served defendant rule in the context of the need for unanimity of consent, a later-served

defendant should have 30 days to consent to removal. The Apotex Defendants did in fact file a Notice of Consent on May 9, 2008, within thirty days of removal on April 11, 2008 [DE 16]. Therefore there is no defect in removal procedure and the motion to remand must be denied.

III. MOTION TO DISMISS

*4 Turning next to the Apotex Defendants motion to dismiss, the Court has addressed this same motion, response and reply in the related case of *Masterson v. Apotex*, Case No. 07-61665-Civ-JIC. The Court will repeat its ruling here.

A. Motion to Dismiss Standard

Until the recent Supreme Court decision in *Bell Atlantic Corp. v. Twombly*, 550 U.S. ----, 127 S.Ct. 1955, 167 L.Ed.2d 929 (2007), courts routinely followed the rule set forth in *Conley v. Gibson*, 355 U.S. 41, 45-46, 78 S.Ct. 99, 2 L.Ed.2d 80 (1957) that, "a complaint should not be dismissed for failure to state a claim unless it appears beyond a doubt that the plaintiff could prove no set of facts in support of his claim which would entitle him to relief."However, pursuant to *Twombly*, to survive a motion to dismiss, a complaint must now contain factual allegations which are "enough to raise a right to relief above the speculative level."127 S.Ct. at 1965. As under *Conley*, a complaint must be liberally construed, assuming the facts alleged therein as true and drawing all reasonable inferences from those facts in the plaintiff's favor. *Id.* at 1964-65.A complaint should not be dismissed simply because the court is doubtful that the plaintiff will be able to prove all of the necessary factual allegations. *Id.* Accordingly, a well-pleaded complaint will survive a motion to dismiss " 'even if it appears that a recovery is very remote and unlikely.' " *Id.* at 1965 (citation omitted). "While a complaint attacked by a Rule 12(b)(6) motion to dismiss does not need detailed factual allegations, a plaintiff's obligation to provide the 'grounds' of his 'entitle[ment] to relief' requires more than labels and conclusions, and a formulaic recitation of the elements of a cause of action will not do." *Id.* at 1964-65.Rather, the facts set forth in the complaint must be sufficient to "nudge the[ ] claims across the line from conceivable to plausible." *Id.* at 1974.

B. FDCA Preemption

"A state law that conflicts with a federal law is preempted under the Supremacy Clause of the United States Constitution, art. VI, cl.2."*Mensing v. Wyeth*, --- F.Supp.2d ----, 2008 WL 2444689 (D.Minn. June 17, 2008). The Apotex Defendants assert that the Plaintiffs' state law claims for negligence, negligent design, strict liability (design), strict liability (failure to warn), and loss of consortium claims are preempted by the Federal Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 21U.S.C. 301-397, and implementing regulations of the Food and Drug Administration ("FDA"). This exact legal question was recently considered by the United States Court of Appeals for the Third Circuit, resulting in the first published opinion by a federal appeals court on this issue. *Colacicco v. Apotex*, 521 F.3d 253 (3rd Cir.2008).

The Third Circuit described in detail in Part II of its opinion the statutory and regulatory provisions that govern FDA approval of newly listed drugs and generic drugs, as well as labeling requirements and post-approval regulation. This Court adopts and incorporates by reference here Part II of the *Colacicco* opinion discussing the FDA regulatory scheme. 521 F.3d at 257-260.

*5 In Part IV of its opinion, the Third Circuit discussed the various preemption theories and the Supreme Court's decisions affecting the preemption analysis. Preemption can be express or implied, with two forms of implied preemption: "field preemption" and "conflict preemption." *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 713, 105 S.Ct. 2371, 85 L.Ed.2d 714 (1985). The FDCA does not contain an express preemption provision. Rather, Defendants assert that because it is impossible to comply with both the FDCA and with state common law regarding failure to warn, the state common law is impliedly preempted under the conflict preemption doctrine.

Traditionally, in implied preemption cases, a presumption against preemption existed where Congress has legislated in a field in which the States have traditionally occupied. *Medtronic v. Lohr*, 518 U.S. 470, 485, 116 S.Ct. 2240, 135 L.Ed.2d 700 (1996). However, recent Supreme Court cases have called this presumption into question in conflict

preemption cases. *Colacicco*, 521 F.3d at 264, citing *United States v. Locke*, 529 U.S. 89, 94, 120 S.Ct. 1135, 146 L.Ed.2d 69 (2000), *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 347-48, 121 S.Ct. 1012, 148 L.Ed.2d 854 (2001) (fraud upon the FDA claim found preempted), *Riegel v. Medtronic, Inc.*, --- U.S. ----, 128 S.Ct. 999, 169 L.Ed.2d 892 (2008) (Medical Device Amendments ("MDA") to FDCA expressly preempt state common law claims-Supreme Court did not discuss preemption presumption as it did in *Lohr*, also an MDA case).

The Apotex Defendants assert, based upon this recent case law, as well as *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 869, 120 S.Ct. 1913, 146 L.Ed.2d 914 (2000),[FN6] that in conflict preemption cases in an area of the law with a long-standing federal presence, there is no presumption against preemption. Plaintiffs argue that states have long legislated in the area of public safety. The *Colacicco* opinion appears to side with the Defendants' view as it stated that "[defendant's] argument that the presumption against preemption is inapplicable in the context of implied conflict preemption has more force."521 F.3d at 265.

> FN6. *Geier* involved an express preemption provision with regard to auto safety that also contained a "savings clause" for state common law tort actions. The Supreme Court found conflict preemption against such tort claims despite the savings clause. 529 U.S. at 881.

The Court hereby adopts this analysis as well, with the conclusion that the presumption against preemption is inapplicable in the context of implied conflict preemption. In addition, the Court agrees with the Third Circuit and those cases that find that the FDA's expressed views on preemption are only "entitled to respect," not the full deference accorded to regulations that have the force of law. Colacicco, 521 F.3d at 274-75, citing *Skidmore v. Swift & Co.*, 323 U.S. 134, 65 S.Ct. 161, 89 L.Ed. 124 (1944).

C. Generic Drugs and Preemption

At this point, having determined that implied preemption of state tort claims regarding failure to warn of certain dangers of prescription drugs could be proper, the facts of this case differ from those present in *Colacicco*. In *Colacicco*, the plaintiffs were suing for failure to warn of the increased dangers of suicide in patients taking Paxil and its generic equivalents. The FDA had specifically considered an additional warning for adult suicidality several times and rejected such a warning. *Id.* at 269.The Third Circuit stated that "a state-law obligation to include a warning asserting the existence of an association between [Paxil] and suicidality directly conflicts with the FDA's oft-repeated conclusion that the evidence did not support such an association."*Id.* at 271.Therefore preemption was proper in *Colacicco* because the FDA had clearly and publicly stated its position that no warning was required prior to the prescriptions and deaths at issue.*Id.*

***6** The Third Circuit specifically did not address the issue relevant to the case at bar concerning whether claims against "generic drug manufacturers are preempted on the basis of their obligations under the Hatch-Waxman Amendments [to the FDCA]."*Id.*Rather, the holding is "limited to circumstances in which the FDA has publicly rejected the need for a warning that plaintiffs argue state law requires."*Id.* at 272.[FN7]

> FN7. The Third Circuit noted that the Supreme Court of Vermont has held that there is no preemption "because federal labeling requirements create a floor, not a ceiling, for state regulation."*Colacicco*, 521 F.3d at 271-72, n. 17,*quoting Levine v. Wyeth*, 944 A.2d 179, ¶ 6 (Vt.2006), *cert. granted*,128 U.S. 1118 (2008).

The Apotex Defendants assert that the result in *Colacicco* supports their argument that the more stringent labeling requirements on generic drugs leave no room for a generic manufacturer to change a label to comport with state law.[FN8] Following Congressional approval of the Hatch-Waxman Act, FDA authority to reject generic drugs is limited. Generic drugs are now approved after filing of an Abbreviated New Drug Application ("ANDA"), in which the manufacturer must show bioequivalency to a listed pioneer drug, but need not submit new safety studies. 21 U.S .C. § 355(j)(2)(A)(iv) and sentence at end of subsection (j)(2) (A). Generic drugs are required to have the same label as the listed drug. 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F. R. § 314.150(b)(10) (regulation allowing FDA to withdraw approval of an ANDA if labeling not

consistent with listed drug).

> FN8. The Court notes that the key factual distinction between the present Paxil birth defect cases and *Colacicco* is that the FDA has never considered a warning with regard to birth defects. However, in the case at bar, only the generic manufacturer is left in the case, so the Court need not consider in this instance whether a failure to warn claim against a manufacturer of Paxil, a listed drug, is preempted.

Apotex further argues that while drug manufacturers of listed drugs have some ability to change or request a change to drug labeling by the FDA, a generic drug must continue to have the same label as the pioneer listed drug to which it is bioequivalent. Compare 21 C.F.R. 314.70(c)(6)(iii)(A) with 21 C.F.R. § 314.150(b)(10). Therefore, if state law regarding failure to warn is not preempted, it would be impossible for Apotex to meet both requirements.

Plaintiffs argue that the Hatch-Waxman Amendments act only to limit FDA actions toward generic manufacturers, but do not diminish Apotex's responsibilities to comply with state law. They argue that Apotex as a generic manufacturer could have sought an exception to the labeling requirements from the FDA to comply with state laws. Plaintiffs argue 21 C.F.R. § 314.150(b)(10) allows certain exceptions to the "same label" requirement. However, those exceptions relate only to whether a new patent was granted on the listed drug or whether a period of exclusivity is accorded to the listed drug. 21 C.F.R. § 314.150(b)(10)(i) and (ii).

Plaintiffs assert that Apotex had an obligation under both federal and state law to disclose all known risks and seek to update its labeling to protect the public safety, regardless of the FDA's limitations. They assert that Defendants could have complied with both state and federal law. They characterize their state law claims as "parallel claims" to the alleged violations of FDA regulations for the failure of Apotex to disclose known risks.

Finally, citing to case law from other Circuits, Plaintiffs assert that the Complaint alleges design defect claims that are not preempted. Even if federal labeling requirements preempt failure to warn claims, the FDA regulatory scheme does not shield manufacturers from liability for defects during the manufacturing or design process.

*7 Following the *Colacicco* opinion, only one district court has considered this exact question whether preemption does apply to claims against a generic manufacturer for failure to warn claims based upon the labeling ("labeling" includes inserts given to patients by physicians and/or pharmacists).[FN9] *Mensing v. Wyeth*, --- F.Supp.2d ----, 2008 WL 2444689 (D.Minn. June 17, 2008) .[FN10] The Minnesota court concluded that a generic manufacturer has no legal duty to propose revised labeling to the FDA, and even if it does voluntarily propose such a change, approval of the change with regard to the generic product and the listed drug is left to the discretion of the FDA.2008 WL 2444689 at *8. Thus, the result of that request would "require speculation about what the FDA might have done."*Id.* Therefore, the Court concluded that imposing an affirmative state law duty to add safety information upon a generic manufacturer would directly conflict with the statutory scheme of the Hatch Waxman Act. *Id.*

> FN9. On July 18, 2008, Plaintiffs submitted a Notice of Supplemental Authority relying upon *Tucker v. SmithKline Beecham Corp.*, 2008 WL 2788505 (S.D.Ind.2008). In *Tucker,* the District Court reversed its earlier ruling dismissing the case on preemption grounds. This case involved a claim for failure to warn of increased suicidality upon ingestion of Paxil, a listed drug (i.e., not a generic drug).

> FN10. Another post-*Colacicco* decision concluded that state law claims were preempted against a generic manufacturer of an over-the-counter ("OTC") drug. *Gaeta v. Perrigo Pharmaceuticals Company*, --- F.Supp.2d ----, 2008 WL 2548813 (N.D.Cal. June 13, 2008). However, as in *Colacicco,* the *Gaeta* decision also mentioned that the FDA had once rejected a warning as to the ibuprofen drug at issue.
>
> A third decision involving similar facts as *Colacicco* also followed that decision. *Mason v. Smithkline Beecham Corp.*, 546

F.Supp.2d 618 (C.D.Ill.2008) (preemption of claims of failure to warn of suicidality for Paxil).

This Court agrees with the analysis and conclusion of the decision in *Mensing* finding preemption of state law failure to warn claims against a generic manufacturer/distributor such as the Apotex Defendants. Because the FDA, pursuant to the FDCA statutory scheme as amended by the Hatch Waxman Act, requires generic drugs to have the same labeling as listed drugs, these federal laws preempt such a state law claim. Unlike a manufacturer of a listed drug, a generic manufacturer has a limited ability to even suggest a labeling change, subject solely to the discretion of the FDA to change the labeling for both the generic and the listed drug. Therefore, compliance with a state law duty to warn would conflict with the federal statutory scheme.

However, this preemption does not extend to manufacturing defect claims that arise separate and apart from a failure to warn claim. Given that the Complaint in this case appears to merge the theories of failure to warn and design/manufacturing defect under broader theories of negligence and strict liability, the Court will grant the present motion to dismiss, without prejudice to Plaintiffs filing an amended complaint separating out the failure to warn, design defect, and manufacturing defect claims.[FN11]

FN11. Plaintiffs may restate their failure to warn claims against the Apotex Defendants in the same document, which though they would be subject to dismissal pursuant to this Order, would allow a cleaner record for appellate purposes, and will allow the same claims to progress against SmithKline Beecham, who remains in this case.

IV. CONCLUSION

Accordingly, it is hereby **ORDERED and ADJUDGED** as follows:

1. Plaintiffs' Motion to Remand and for Attorneys Fees and Costs is hereby **DENIED** [DE 15];

2. Defendants Apotex Corp. and Apotex Inc.'s Motion to Dismiss [DE 6] is hereby **GRANTED in part** as to failure to warn claims, but **DENIED** as to design defect and manufacturing defect claims;

3. Plaintiffs shall file an Amended Complaint by August 29, 2008 pursuant to this Order;

4. The parties should submit a proposed scheduling order by August 29, 2008 regarding the parties' suggestions as to a trial date and pretrial deadlines.

DONE AND ORDERED.

S.D.Fla.,2008.
Bolin ex rel. Bolin v. SmithKline Beecham Corp.
Slip Copy, 2008 WL 3286973 (S.D.Fla.)

END OF DOCUMENT

EXHIBIT B

Westlaw.
Slip Copy
Slip Copy, 2008 WL 3262690 (S.D.Fla.)

HMasterson v. Apotex, Corp.
S.D.Fla.,2008.
Only the Westlaw citation is currently available.
United States District Court,S.D. Florida.
Heather MASTERSON, individually, and as guardian on behalf of Zachary Gratton, a minor, Plaintiff,
v.
APOTEX, CORP., Apotex, Inc., et al., Defendants.
No. 07-61665-CIV.

Aug. 7, 2008.

Bryan Frederick Aylstock, Douglass Alan Kreis, Joshua A. Jones, Aylstock Witkin Kreis & Overholtz PLLC, Pensacola, FL, for Plaintiff.
Michael Alexandar Garcia, Fowler White Burnett, Miami, FL, for Defendants.

ORDER GRANTING MOTION TO DISMISS ORDER TO SHOW CAUSE WHY UNSERVED DEFENDANTS SHOULD NOT BE DISMISSED

JAMES I. COHN, District Judge.
*1 THIS CAUSE is before the Court upon the Apotex Defendants' Motions to Dismiss [DE 32/34], their Memorandum filed in support of the Motions [DE 36], the Plaintiffs' Response thereto [DE 62], Defendants' Reply [DE 67], and the parties' Notices of Supplemental Authority [DE's 74/75] submitted pursuant to the Court's "Minute Order" of May 13, 2008 [DE 71]. The Court has carefully considered all the filings, and is otherwise fully advised in the premises.

I. BACKGROUND

Plaintiffs filed this action in Broward County Circuit Court alleging various claims of negligence and product liability against manufacturers and/or distributors of a psychopharmaceutical drug that is alleged to have caused birth defects in the minor child in this case. Plaintiff Heather Masterson was prescribed and ingested the brand name drug Paxil, as well as its generic equivalents, during her pregnancy. Plaintiffs allege that Defendants failed to warn Plaintiff Masterson of the possible tetragenic effects of the drugs on her then unborn child. Her child, Zachary Gratton, was born with certain birth defects, which she alleges were caused by her ingestion of Paxil and the generics.

The regulatory scheme for approval of brand name drugs ("pioneer" or "listed" drugs) and their generic equivalents give the FDA significant authority to approve drugs and their warning labels. Defendant Apotex Corporation and Defendant Apotex, Inc. (collectively, "Apotex Defendants" or "Apotex") manufacture and distribute the generic product. Both Paxil and its generic equivalents were approved for use by the FDA and used the FDA-approved warning label, which did not warn against side effects to children during pregnancy.

Defendant SmithKline Beecham, manufacturer of Paxil, removed this case to this Court. The Court recently denied Plaintiff's motion to remand. Although Smithkline was dismissed from this case, Apotex moved to dismiss the Complaint on federal preemption grounds. The parties have fully briefed the motion, as well as filed Notices of Supplemental Authority in response to the Court's request following the United States Court of Appeals for the Third Circuit's decision in *Colacicco v. Apotex*, 521 F.3d 253 (3rd Cir.2008).

II. DISCUSSION

A. Motion to Dismiss Standard

Until the recent Supreme Court decision in *Bell Atlantic Corp. v. Twombly*, 550 U.S. ----, 127 S.Ct. 1955, 167 L.Ed.2d 929 (2007), courts routinely followed the rule set forth in *Conley v. Gibson*, 355 U.S. 41, 45-46, 78 S.Ct. 99, 2 L.Ed.2d 80 (1957) that, "a complaint should not be dismissed for failure to state a claim unless it appears beyond a doubt that the plaintiff could prove no set of facts in support of his claim which would entitle him to relief."However, pursuant to *Twombly*, to survive a motion to dismiss, a complaint must now contain factual allegations which are "enough to raise a right to relief above the speculative level."127 S.Ct. at 1965. As under *Conley*, a complaint must be liberally construed, assuming the facts alleged therein as true and

drawing all reasonable inferences from those facts in the plaintiff's favor. *Id.* at 1964-65.A complaint should not be dismissed simply because the court is doubtful that the plaintiff will be able to prove all of the necessary factual allegations. *Id.* Accordingly, a well-pleaded complaint will survive a motion to dismiss " 'even if it appears that a recovery is very remote and unlikely.' " *Id.* at 1965 (citation omitted). "While a complaint attacked by a Rule 12(b)(6) motion to dismiss does not need detailed factual allegations, a plaintiff's obligation to provide the 'grounds' of his 'entitle[ment] to relief' requires more than labels and conclusions, and a formulaic recitation of the elements of a cause of action will not do." *Id.* at 1964-65.Rather, the facts set forth in the complaint must be sufficient to "nudge the[ ] claims across the line from conceivable to plausible." *Id.* at 1974.

B. FDCA Preemption

***2** "A state law that conflicts with a federal law is preempted under the Supremacy Clause of the United States Constitution, art. VI, cl.2."*Mensing v. Wyeth,* ---- F.Supp.2d ----, 2008 WL 2444689 (D.Minn. June 17, 2008). The Apotex Defendants assert that the Plaintiffs' state law claims for negligence, negligent design, strict liability (design), strict liability (failure to warn), and loss of consortium claims are preempted by the Federal Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 21U.S.C. 301-397, and implementing regulations of the Food and Drug Administration ("FDA"). This exact legal question was recently considered by the United States Court of Appeals for the Third Circuit, resulting in the first published opinion by a federal appeals court on this issue. *Colocicco v. Apotex,* 521 F.3d 253 (3rd Cir.2008).

The Third Circuit described in detail in Part II of its opinion the statutory and regulatory provisions that govern FDA approval of newly listed drugs and generic drugs, as well as labeling requirements and post-approval regulation. This Court adopts and incorporates by reference here Part II of the *Colacicco* opinion discussing the FDA regulatory scheme. 521 F.3d at 257-260.

In Part IV of its opinion, the Third Circuit discussed the various preemption theories and the Supreme Court's decisions affecting the preemption analysis. Preemption can be express or implied, with two forms of implied preemption: "field preemption" and "conflict preemption." *Hillsborough County v. Automated Med. Labs.,* Inc., 471 U.S. 707, 713, 105 S.Ct. 2371, 85 L.Ed.2d 714 (1985). The FDCA does not contain an express preemption provision. Rather, Defendants assert that because it is impossible to comply with both the FDCA and with state common law regarding failure to warn, the state common law is impliedly preempted under the conflict preemption doctrine.

Traditionally, in implied preemption cases, a presumption against preemption existed where Congress has legislated in a field in which the States have traditionally occupied. *Medtronic v. Lohr,* 518 U.S. 470, 485, 116 S.Ct. 2240, 135 L.Ed.2d 700 (1996). However, recent Supreme Court cases have called this presumption into question in conflict preemption cases. *Colacicco,* 521 F.3d at 264, citing *United States v. Locke,* 529 U.S. 89, 94, 120 S.Ct. 1135, 146 L.Ed.2d 69 (2000), *Buckman Co. v. Plaintiffs' Legal Comm.,* 531 U.S. 341, 347-48, 121 S.Ct. 1012, 148 L.Ed.2d 854 (2001) (fraud upon the FDA claim found preempted), *Riegel v. Medtronic, Inc.,* --- U.S. ----, 128 S.Ct. 999, 169 L.Ed.2d 892 (2008) (Medical Device Amendments ("MDA") to FDCA expressly preempt state common law claims-Supreme Court did not discuss preemption presumption as it did in *Lohr,* also an MDA case).

The Apotex Defendants assert, based upon this recent case law, as well as *Geier v. Am. Honda Motor Co.,* 529 U.S. 861, 869, 120 S.Ct. 1913, 146 L.Ed.2d 914 (2000),[FN1] that in conflict preemption cases in an area of the law with a long-standing federal presence, there is no presumption against preemption. Plaintiffs argue that states have long legislated in the area of public safety. The *Colacicco* opinion appears to side with the Defendants' view as it stated that "[defendant's] argument that the presumption against preemption is inapplicable in the context of implied conflict preemption has more force."521 F.3d at 265.

> FN1.*Geier* involved an express preemption provision with regard to auto safety that also contained a "savings clause" for state common law tort actions. The Supreme Court found conflict preemption against such tort claims despite the savings clause. 529 U.S. at 881.

***3** The Court hereby adopts this analysis as well, with the conclusion that the presumption against preemption is inapplicable in the context of implied conflict preemption. In addition, the Court agrees with the Third Circuit and those cases that find that the FDA's expressed views on preemption are only "entitled to respect," not the full deference accorded to regulations that have the force of law. Colacicco, 521 F.3d at 274-75, citing *Skidmore v. Swift & Co.*, 323 U.S. 134, 65 S.Ct. 161, 89 L.Ed. 124 (1944).

C. Generic Drugs and Preemption

At this point, having determined that implied preemption of state tort claims regarding failure to warn of certain dangers of prescription drugs could be proper, the facts of this case differ from those present in *Colacicco.*In *Colacicco,* the plaintiffs were suing for failure to warn of the increased dangers of suicide in patients taking Paxil and its generic equivalents. The FDA had specifically considered an additional warning for adult suicidality several times and rejected such a warning. *Id.* at 269.The Third Circuit stated that "a state-law obligation to include a warning asserting the existence of an association between [Paxil] and suicidality directly conflicts with the FDA's oft-repeated conclusion that the evidence did not support such an association."*Id.* at 271.Therefore preemption was proper in *Colacicco* because the FDA had clearly and publicly stated its position that no warning was required prior to the prescriptions and deaths at issue.*Id.*

The Third Circuit specifically did not address the issue relevant to the case at bar concerning whether claims against "generic drug manufacturers are preempted on the basis of their obligations under the Hatch-Waxman Amendments [to the FDCA]."*Id.*Rather, the holding is "limited to circumstances in which the FDA has publicly rejected the need for a warning that plaintiffs argue state law requires."*Id.* at 272.[FN2]

> FN2. The Third Circuit noted that the Supreme Court of Vermont has held that there is no preemption "because federal labeling requirements create a floor, not a ceiling, for state regulation."*Colacicco,* 521 F.3d at 271-72, n. 17,*quoting Levine v. Wyeth,* 944 A.2d 179, ¶ 6 (Vt.2006), *cert. granted,*128 U.S. 1118 (2008).

The Apotex Defendants assert that the result in *Colacicco* supports their argument that the more stringent labeling requirements on generic drugs leave no room for a generic manufacturer to change a label to comport with state law.[FN3] Following Congressional approval of the Hatch-Waxman Act, FDA authority to reject generic drugs is limited. Generic drugs are now approved after filing of an Abbreviated New Drug Application ("ANDA"), in which the manufacturer must show bioequivalency to a listed pioneer drug, but need not submit new safety studies. 21 U.S .C. § 355(j)(2)(A)(iv) and sentence at end of subsection (j)(2) (A). Generic drugs are required to have the same label as the listed drug. 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F. R. § 314.150(b)(10) (regulation allowing FDA to withdraw approval of an ANDA if labeling not consistent with listed drug).

> FN3. The Court notes that the key factual distinction between the present Paxil birth defect cases and ***Colacicco*** is that the FDA has never considered a warning with regard to birth defects. However, in the case at bar, only the generic manufacturer is left in the case, so the Court need not consider in this instance whether a failure to warn claim against a manufacturer of Paxil, a listed drug, is preempted.

Apotex further argues that while drug manufacturers of listed drugs have some ability to change or request a change to drug labeling by the FDA, a generic drug must continue to have the same label as the pioneer listed drug to which it is bioequivalent. Compare 21 C.F.R. 314.70(c)(6)(iii)(A) with 21 C.F.R. § 314.150(b)(10). Therefore, if state law regarding failure to warn is not preempted, it would be impossible for Apotex to meet both requirements.

***4** Plaintiffs argue that the Hatch-Waxman Amendments act only to limit FDA actions toward generic manufacturers, but do not diminish Apotex's responsibilities to comply with state law. They argue that Apotex as a generic manufacturer could have sought an exception to the labeling requirements from the FDA to comply with state laws. Plaintiffs argue 21 C.F.R. § 314.150(b)(10) allows certain exceptions to the "same label" requirement.

However, those exceptions relate only to whether a new patent was granted on the listed drug or whether a period of exclusivity is accorded to the listed drug. 21 C.F.R. § 314.150(b)(10)(i) and (ii).

Plaintiffs assert that Apotex had an obligation under both federal and state law to disclose all known risks and seek to update its labeling to protect the public safety, regardless of the FDA's limitations. They assert that Defendants could have complied with both state and federal law. They characterize their state law claims as "parallel claims" to the alleged violations of FDA regulations for the failure of Apotex to disclose known risks.

Finally, citing to case law from other Circuits, Plaintiffs assert that the Complaint alleges design defect claims that are not preempted. Even if federal labeling requirements preempt failure to warn claims, the FDA regulatory scheme does not shield manufacturers from liability for defects during the manufacturing or design process.

Following the *Colacicco* opinion, only one district court has considered this exact question whether preemption does apply to claims against a generic manufacturer for failure to warn claims based upon the labeling ("labeling" includes inserts given to patients by physicians and/or pharmacists).[FN4] *Mensing v. Wyeth*, --- F.Supp.2d ----, 2008 WL 2444689 (D.Minn. June 17, 2008) .[FN5] The Minnesota court concluded that a generic manufacturer has no legal duty to propose revised labeling to the FDA, and even if it does voluntarily propose such a change, approval of the change with regard to the generic product and the listed drug is left to the discretion of the FDA.2008 WL 2444689 at *8. Thus, the result of that request would "require speculation about what the FDA might have done."*Id.* Therefore, the Court concluded that imposing an affirmative state law duty to add safety information upon a generic manufacturer would directly conflict with the statutory scheme of the Hatch Waxman Act. *Id.*

FN4. On July 18, 2008, Plaintiffs submitted a Notice of Supplemental Authority relying upon *Tucker v. SmithKline Beecham Corp.*, 2008 WL 2788505 (S.D.Ind.2008). In *Tucker*, the District Court reversed its earlier ruling dismissing the case on preemption grounds. This case involved a claim for failure to warn of increased suicidality upon ingestion of Paxil, a listed drug (i.e., not a generic drug).

FN5. Another post-*Colacicco* decision concluded that state law claims were preempted against a generic manufacturer of an over-the-counter ("OTC") drug. *Gaeta v. Perrigo Pharmaceuticals Company*, --- F.Supp.2d ----, 2008 WL 2548813 (N.D.Cal. June 13, 2008). However, as in *Colacicco*, the *Gaeta* decision also mentioned that the FDA had once rejected a warning as to the ibuprofen drug at issue.

A third decision involving similar facts as *Colacicco* also followed that decision. *Mason v. Smithkline Beecham Corp.*, 546 F.Supp.2d 618 (C.D.Ill.2008) (preemption of claims of failure to warn of suicidality for Paxil).

This Court agrees with the analysis and conclusion of the decision in *Mensing* finding preemption of state law failure to warn claims against a generic manufacturer/distributor such as the Apotex Defendants. Because the FDA, pursuant to the FDCA statutory scheme as amended by the Hatch Waxman Act, requires generic drugs to have the same labeling as listed drugs, these federal laws preempt such a state law claim. Unlike a manufacturer of a listed drug, a generic manufacturer has a limited ability to even suggest a labeling change, subject solely to the discretion of the FDA to change the labeling for both the generic and the listed drug. Therefore, compliance with a state law duty to warn would conflict with the federal statutory scheme.

***5** However, this preemption does not extend to manufacturing defect claims that arise separate and apart from a failure to warn claim. Given that the Complaint in this case appears to merge the theories of failure to warn and design/manufacturing defect under broader theories of negligence and strict liability, the Court will grant the present motion to dismiss, without prejudice to Plaintiffs filing an amended complaint separating out the failure to warn, design defect, and manufacturing defect claims.[FN6]

FN6. Plaintiffs may restate their failure to warn claims in the same document, which though they would be subject to dismissal pursuant to this Order, would allow a cleaner record for appellate purposes.

III. CONCLUSION

Accordingly, it is hereby **ORDERED and ADJUDGED** as follows:

1. The Apotex Defendants' Motion to Dismiss [DE 32] is hereby **DENIED** as moot, as a duplicate docket entry;

2. The Apotex Defendants' Motion to Dismiss [DE 34] is hereby **GRANTED** in **part** as to failure to warn claims, but **DENIED** as to design defect and manufacturing defect claims;

3. Defendant SmithKline Beecham's Joint Motion to Continue [DE 17] is hereby **DENIED** as moot;

4. Plaintiffs shall file an Amended Complaint by August 29, 2008 pursuant to this Order;

5. Plaintiffs shall show cause by August 29, 2008, why unserved Defendants Alpha Pharm Party Ltd., a/k/a Alphapharm, and Teva Pharmaceuitical lndustries Ltd, a/k/a Teva Pharmaceutical USA, Inc., should not be dismissed for failure to serve.

6. Failure to timely show cause shall result in dismissal of these defendants for failure to serve.

DONE AND ORDERED.

S.D.Fla.,2008.
Masterson v. Apotex, Corp.
Slip Copy, 2008 WL 3262690 (S.D.Fla.)

END OF DOCUMENT

EXHIBIT C

Valerio ex rel. Valerio v. SmithKline Beecham Corp.
S.D.Fla.,2008.
Only the Westlaw citation is currently available.
United States District Court,S.D. Florida.
Alena A. VALERIO, a minor by Christina M. VALERIO and Luis C. Valerio, III, and Christina M. Valerio and Luis C. Valerio, III, Individually,
Plaintiffs,
v.
SMITHKLINE BEECHAM CORPORATION d/b/a Glaxosmithkline, a Pennsylvania corporation, Apotex Corp. and Apotex, Inc., Defendants.
No. 08-60522-CIV.

Aug. 7, 2008.

Bryan Frederick Aylstock, Joshua A. Jones, Aylstock, Witkin, Kreis & Overholtz, PLLC, Pensacola, FL, Jennifer R. Liakos, Karen Barth Menzies, Baum Hedlund, Kate E. Gillespie, Ronald L.M. Goldman, Baum, Hedlund, Aristel & Goldman, P.C., Los Angeles, CA, for Plaintiffs.
Maria Helena Ruiz, Mercer Kaye Clarke, Clarke, Silverglate & Campbell, P.A., Michael Alexandar Garcia, Fowler White Burnett, Miami, FL, for Defendants.

ORDER DENYING MOTION TO REMAND ORDER GRANTING IN PART MOTION TO DISMISS

JAMES I. COHN, District Judge.
***1** THIS CAUSE is before the Court upon Plaintiffs' Motion to Remand and Motion for Attorneys Fees and Costs [DE 15] and Defendants Apotex Corp. and Apotex Inc.'s Motion to Dismiss [DE 8]. The Court has carefully considered the motions, responses and replies thereto, and is otherwise fully advised in the premises.[FN1]

FN1. Plaintiffs did not file a reply in support of their motion to remand.

I. BACKGROUND

Plaintiffs filed this action in Broward County Circuit Court alleging various claims of negligence and product liability against manufacturers and/or distributors of a psychopharmaceutical drug that is alleged to have caused birth defects in the minor child in this case. Plaintiffs are residents and citizens of Arizona. Defendant Smith klineBeecham Corporation is a citizen of Pennsylvania. Defendant Apotex Corporation ("Apotex Corp.") has its principal place of business in Weston, Florida, and is a wholly owned subsidiary of Defendant Apotex, Inc., a Canadian corporation (collectively, "Apotex Defendants").

On April 11, 2008, prior to being served, Defendant SmithKline Beecham removed this case to this Court. The Florida defendant, Apotex Corp., was not served until April 16, 2008. On April 25, 2008, the Apotex Defendants moved to dismiss this case based upon federal preemption. On May 9, 2008, Plaintiffs moved to remand the case pursuant to 28 U.S.C. § 1441(b), the "forum-state defendant rule" because a Florida defendant, Apotex Corp., is in the case. Defendants oppose the motion to remand

II. MOTION TO REMAND

On a motion to remand, the removing party bears the burden of establishing jurisdiction. *Tapscott v. M.S. Dealer Serv. Corp.*, 77 F.3d 1353, 1356 (11th cir.1996), *overruled on other grounds by Cohen v. Office Depot, Inc.*, 204 F.3d 1069, 1076 (11th Cir.2000); *Diaz v. Sheppard*, 85 F.3d 1502, 1505 (11th Cir.1996). In this case, there is no dispute that complete diversity exists, both now and at the time of removal. However, Plaintiffs seek remand because pursuant to 28 U.S.C. § 1441(b), a forum state defendant cannot remove an action. The statute states that for diversity jurisdiction, any "such action shall be removable only if none of the parties in interest **properly joined and served** as defendants is a citizen of the State in which such action is brought."28 U.S.C. § 1441(b) (emphasis added). Thus, even though a federal court may have original jurisdiction over an action, the forum defendant rule forbids removal of such action.

A. Forum Defendant Rule[FN2]

FN2. This Court previously addressed this issue in *Masterson v. Apotex, et al,* 2008 WL 2047979 (S.D.Fla.2008) (Case No. 07-61665-Civ). The Court repeats most of that decision herein.

Plaintiff states that the United States Court of Appeals for the Eleventh Circuit precedent, as well as Supreme Court precedent, mandate remand in this case. However, Plaintiff has incorrectly equated diversity jurisdiction with the forum defendant rule's ban on removal of certain cases that otherwise meet the diversity jurisdiction requirement. *Hurley v. Motor Coach Industries, Inc.*, 222 F.3d 377, 379-380 (7th Cir.2000) (forum defendant rule is not jurisdictional); *Snapper, Inc. v. Redan*, 171 F.3d 1249, 1258 (11th Cir.1999). Thus, Plaintiff's reliance on decisions questioning diversity jurisdiction cases is not determinative of this forum defendant issue.*Florence v. Crescent Resources, LLC*, 484 F.3d 1293, 1297 (11th Cir.2007); *Tillman v. R.J. Reynolds Tobacco*, 253 F.3d 1302, 1305 (11th Cir.2001). Moreover, in this case there is no issue of fraudulent joinder, no non-diverse defendant, and diversity jurisdiction is clearly present.

***2** Where complete diversity exists, it is unclear whether the inclusion of an unserved resident defendant defeats removal under 28 U.S.C. § 1441(b).[FN3] The plain language of the statute requires the resident defendant to be "properly joined and served" to defeat removal. 28 U.S.C. § 1441(b). Thus, the present situation is distinguishable from cases where "the existence of diversity is determined from the fact of citizenship of the parties named and not from the fact of service."*New York Life Ins. Co. v. Deshotel*, 142 F.3d 873, 883 (5th Cir.1998). Rather, in the more specific context of the forum-state defendant rule in § 1441(b), Congress has apparently determined that the Court only look at "properly joined and served" defendants. At least in passing, one Circuit Court of Appeals agrees with this conclusion. *McCall v. Scott*, 239 F.3d 808, 813, n. 2 (6th Cir.2001).

FN3. Where there is no issue of fraudulent joinder of a defendant, the forum defendant rule does not arise often. It can only arise, as in this case, when plaintiffs are not "forum state" citizens.

The district court decisions on this issue are split. Defendants rely upon *Ott v. Consolidated Freightways Corporation*, 213 F.Supp.2d 662, 665 (S.D.Miss.2002), which answers the precise question of this case by concluding that unserved defendants at the time of removal may be ignored for § 1441(b) purposes. Other cited cases following Ott are cited as well. *Stan Winston Creatures, Inc. v. Toys "R" Us, Inc.*, 314 F.Supp.2d 177, 180-81 (S.D.N.Y.2003) (case remanded because defendant in question was in fact served, but legal conclusion of *Ott* followed); *Clawson v. FedEx Ground Package System, Inc.*, 451 F.Supp.2d 731, 735-36 (D.Md.2006).

In the only published, non-fraudulent joinder decision cited by Plaintiffs, [FN4] the Court in *Oxendine v. Merck and Co., Inc.*, 236 F.Supp.2d 517, 524-25 (D.Md.2002), held that because the law prior to enactment of § 1441(b) stated that where a non-separable controversy involves a resident defendant, the fact that the resident defendant has not been served with process does not justify removal by the non-resident defendant. However, this Court agrees with the decisions concluding that § 1441(b) as amended limits looking only at "properly joined and served" defendants at the time of removal where diversity jurisdiction is not an issue.

FN4. In its research, the Court uncovered a Circuit Court of Appeals' description of the district court decision under review in *Holmstrom v. Peterson*, 492 F.3d 383, 385 (7th Cir.2007), wherein the lower court recognized that the plain language of the statute required the forum defendant to be properly served to defeat removal, but still held that because there was no indication that plaintiff in that case named the forum state defendant solely to defeat removal, it granted the motion to remand. The Seventh Circuit concluded it lacked jurisdiction to review this procedural defect for other reasons.

Plaintiffs also raise policy concerns regarding acceptance of Defendants' arguments. However, in addition to the statutory language and case law, policy considerations also support Defendants. Removal is "intended to protect out-of-state defendants from possible prejudices in state court."*Lively v. Wild Oats Markets, Inc.*, 456 F.3d

933, 940 (9th Cir.2006). The purpose of the forum state defendant rule is to allow plaintiffs to choose a forum because a forum state defendant does not need the protection of removal rights. However, in the limited situations such as the present case when a non-forum state defendant removes a case also involving a forum defendant, it is necessary to only consider properly served defendants so as to not allow a plaintiff to thwart removal rights of diverse, non forum state defendants by not serving the forum state defendant.[FN5]To avoid this result, plaintiffs can control the situation by attempting immediate service upon a forum state defendant when filing such a case in state court.

> FN5. Plaintiffs also rely upon a series of unpublished decisions from the Eastern District of Pennsylvania involving some of the same parties as the present case. *Takia Malone v. GlaxoSmithKline PLC,* et al, Case No. 07-5048, Order at docket entry 4 (December 4, 2007). However, in *Malone,* Smith KlineBeecham was both the forum state defendant and the removing defendant. The Court there concluded that allowing removal because Smith KlineBeecham was not yet served would defeat congressional intent, citing to *Oxendine.*This Court not only disagrees with *Oxendine,* but factually distinguishes the Pennsylvania cases because in the present case the removing defendant was not the forum-state defendant.

B. Lack of Complete Consent and Amount in Controversy

***3** Plaintiffs also argue that removal was improper because the Apotex Defendants did not consent to removal and the amount in controversy does not satisfy subject matter jurisdiction. Turning to the amount in controversy, because the plaintiff's state court complaint seeks an unspecified amount of damages, the defendant must establish the amount in controversy by a preponderance of the evidence. *Tapscott,* 77 F.3d 1359-60.Defendants argue that the Complaint's allegations of pulmonary stenosis in the minor child and "serious cardiovascular disorder," make it more likely than not that the damages will be over $75,000. Complaint, ¶¶ 25, 36. Plaintiffs seek damages for pecuniary loss, loss of consortium, general and medical damages and related expenses, and punitive damages. Complaint, ¶¶ 37, 41-43, 53-55, 61-63, 69-71, 81-83. The Court can conclude that these damage allegations alone meet Defendants' burden to show that the amount in controversy is greater than $75,000.

Turning next to Plaintiff's argument regarding lack of unanimity of consent, an exception to the unanimity requirement is lack of service upon the other defendants. *White v. Bombardier Corp.,* 313 F.Supp.2d 1295, 1299-1300 (N.D.Fla.2004), citing *Murphy Bros., Inc. v. Michetti Pipe Stringing, Inc.,* 526 U.S. 344, 354, 119 S.Ct. 1322, 143 L.Ed.2d 448 (1999). However, there is a split in the case law in cases where multiple defendants are served at different times. Some courts follow the "first-served" defendant rule, which requires a later-served defendant to remove or consent to removal within thirty days of service upon the first-served defendant, even if more than thirty days has passed, while others have held that a later-served defendant has thirty days from its receipt of service to remove with consent of the others. *Smith v. The Health Center of Lake City, Inc.,* 252 F.Supp.2d 1336, 1341-1345 (M.D.Fla.2003) (collecting cases).

In a recent published decision, the United States Court of Appeals for the Eleventh Circuit adopted the later-served defendant rule. *Bailey v. Janssen Pharmaceutica, Inc.,* --- F.3d ----, 2008 WL 2894742 (11th Cir. July 29, 2008). The Court held that the first-served defendant rule deprives later-served defendants of their right to remove a case, and imposes the word "first" into the plain language of 28 U.S.C. § 1446(b). The Eleventh Circuit followed the trend of the other Circuit Court of Appeals who have considered the issue.*McKinney v. Board of Trustees of Mayland Cmty. College,* 955 F.2d 924, 926-27 (4th Cir.1992); *Brierly v. Alusuisse Flexible Packaging, Inc.,* 184 F.3d 527, 533 (6th Cir.1999); *Marano Enterprises of Kansas v. Z-Teca Restaurants, L.P.,* 254 F.3d 753, 755-56 (8th Cir.2001).

Applying the later-served defendant rule to this case requires one more step. Here, the case was removed even before service. However, using the reasoning of the later-served defendant rule in the context of the need for unanimity of consent, a later-served defendant should have 30 days to consent to removal. The Apotex Defendants did in fact file a Notice of

Consent on May 9, 2008, within thirty days of removal on April 11, 2008 [DE 16]. Therefore there is no defect in removal procedure and the motion to remand must be denied.

III. MOTION TO DISMISS

*4 Turning next to the Apotex Defendants' motion to dismiss, the Court has addressed this same motion, response and reply in the related case of *Masterson v. Apotex,* Case No. 07-61665-Civ-JIC. The Court will repeat its ruling here.

A. Motion to Dismiss Standard

Until the recent Supreme Court decision in *Bell Atlantic Corp. v. Twombly,* 550 U.S. ----, 127 S.Ct. 1955, 167 L.Ed.2d 929 (2007), courts routinely followed the rule set forth in *Conley v. Gibson,* 355 U.S. 41, 45-46, 78 S.Ct. 99, 2 L.Ed.2d 80 (1957) that, "a complaint should not be dismissed for failure to state a claim unless it appears beyond a doubt that the plaintiff could prove no set of facts in support of his claim which would entitle him to relief."However, pursuant to *Twombly,* to survive a motion to dismiss, a complaint must now contain factual allegations which are "enough to raise a right to relief above the speculative level."127 S.Ct. at 1965. As under *Conley,* a complaint must be liberally construed, assuming the facts alleged therein as true and drawing all reasonable inferences from those facts in the plaintiff's favor. *Id.* at 1964-65.A complaint should not be dismissed simply because the court is doubtful that the plaintiff will be able to prove all of the necessary factual allegations. *Id.* Accordingly, a well-pleaded complaint will survive a motion to dismiss " 'even if it appears that a recovery is very remote and unlikely.' " *Id.* at 1965 (citation omitted). "While a complaint attacked by a Rule 12(b)(6) motion to dismiss does not need detailed factual allegations, a plaintiff's obligation to provide the 'grounds' of his 'entitle[ment] to relief' requires more than labels and conclusions, and a formulaic recitation of the elements of a cause of action will not do." *Id.* at 1964-65.Rather, the facts set forth in the complaint must be sufficient to "nudge the[ ] claims across the line from conceivable to plausible." *Id.* at 1974.

B. FDCA Preemption

"A state law that conflicts with a federal law is preempted under the Supremacy Clause of the United States Constitution, art. VI, cl.2."*Mensing v. Wyeth,* --- F.Supp.2d ----, 2008 WL 2444689 (D.Minn. June 17, 2008). The Apotex Defendants assert that the Plaintiffs' state law claims for negligence, negligent design, strict liability (design), strict liability (failure to warn), and loss of consortium claims are preempted by the Federal Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 21U.S.C. 301-397, and implementing regulations of the Food and Drug Administration ("FDA"). This exact legal question was recently considered by the United States Court of Appeals for the Third Circuit, resulting in the first published opinion by a federal appeals court on this issue. *Colacicco v. Apotex,* 521 F.3d 253 (3rd Cir.2008).

The Third Circuit described in detail in Part II of its opinion the statutory and regulatory provisions that govern FDA approval of newly listed drugs and generic drugs, as well as labeling requirements and post-approval regulation. This Court adopts and incorporates by reference here Part II of the *Colacicco* opinion discussing the FDA regulatory scheme. 521 F.3d at 257-260.

*5 In Part IV of its opinion, the Third Circuit discussed the various preemption theories and the Supreme Court's decisions affecting the preemption analysis. Preemption can be express or implied, with two forms of implied preemption: "field preemption" and "conflict preemption." *Hillsborough County v. Automated Med. Labs., Inc.,* 471 U.S. 707, 713, 105 S.Ct. 2371, 85 L.Ed.2d 714 (1985). The FDCA does not contain an express preemption provision. Rather, Defendants assert that because it is impossible to comply with both the FDCA and with state common law regarding failure to warn, the state common law is impliedly preempted under the conflict preemption doctrine.

Traditionally, in implied preemption cases, a presumption against preemption existed where Congress has legislated in a field in which the States have traditionally occupied. *Medtronic v. Lohr,* 518 U.S. 470, 485, 116 S.Ct. 2240, 135 L.Ed.2d 700 (1996). However, recent Supreme Court cases have called this presumption into question in conflict preemption cases. *Colacicco,* 521 F.3d at 264, citing *United States v. Locke,* 529 U.S. 89, 94, 120 S.Ct.

1135, 146 L.Ed.2d 69 (2000), *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 347-48, 121 S.Ct. 1012, 148 L.Ed.2d 854 (2001) (fraud upon the FDA claim found preempted), *Riegel v. Medtronic, Inc.*, --- U.S. ----, 128 S.Ct. 999, 169 L.Ed.2d 892 (2008) (Medical Device Amendments ("MDA") to FDCA expressly preempt state common law claims-Supreme Court did not discuss preemption presumption as it did in *Lohr*, also an MDA case).

The Apotex Defendants assert, based upon this recent case law, as well as *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 869, 120 S.Ct. 1913, 146 L.Ed.2d 914 (2000),[FN6] that in conflict preemption cases in an area of the law with a long-standing federal presence, there is no presumption against preemption. Plaintiffs argue that states have long legislated in the area of public safety. The *Colacicco* opinion appears to side with the Defendants' view as it stated that "[defendant's] argument that the presumption against preemption is inapplicable in the context of implied conflict preemption has more force."521 F.3d at 265.

> FN6.*Geier* involved an express preemption provision with regard to auto safety that also contained a "savings clause" for state common law tort actions. The Supreme Court found conflict preemption against such tort claims despite the savings clause. 529 U.S. at 881.

The Court hereby adopts this analysis as well, with the conclusion that the presumption against preemption is inapplicable in the context of implied conflict preemption. In addition, the Court agrees with the Third Circuit and those cases that find that the FDA's expressed views on preemption are only "entitled to respect," not the full deference accorded to regulations that have the force of law. Colacicco, 521 F.3d at 274-75, citing *Skidmore v. Swift & Co.*, 323 U.S. 134, 65 S.Ct. 161, 89 L.Ed. 124 (1944).

C. Generic Drugs and Preemption

At this point, having determined that implied preemption of state tort claims regarding failure to warn of certain dangers of prescription drugs could be proper, the facts of this case differ from those present in *Colacicco*.In *Colacicco,* the plaintiffs were suing for failure to warn of the increased dangers of suicide in patients taking Paxil and its generic equivalents. The FDA had specifically considered an additional warning for adult suicidality several times and rejected such a warning. *Id.* at 269.The Third Circuit stated that "a state-law obligation to include a warning asserting the existence of an association between [Paxil] and suicidality directly conflicts with the FDA's oft-repeated conclusion that the evidence did not support such an association."*Id.* at 271.Therefore preemption was proper in *Colacicco* because the FDA had clearly and publicly stated its position that no warning was required prior to the prescriptions and deaths at issue.*Id.*

***6** The Third Circuit specifically did not address the issue relevant to the case at bar concerning whether claims against "generic drug manufacturers are preempted on the basis of their obligations under the Hatch-Waxman Amendments [to the FDCA]."*Id.*Rather, the holding is "limited to circumstances in which the FDA has publicly rejected the need for a warning that plaintiffs argue state law requires."*Id.* at 272.[FN7]

> FN7. The Third Circuit noted that the Supreme Court of Vermont has held that there is no preemption "because federal labeling requirements create a floor, not a ceiling, for state regulation."*Colacicco*, 521 F.3d at 271-72, n. 17,*quoting Levine v. Wyeth*, 944 A.2d 179, ¶ 6 (Vt.2006), *cert. granted,*128 U.S. 1118 (2008).

The Apotex Defendants assert that the result in *Colacicco* supports their argument that the more stringent labeling requirements on generic drugs leave no room for a generic manufacturer to change a label to comport with state law.[FN8] Following Congressional approval of the Hatch-Waxman Act, FDA authority to reject generic drugs is limited. Generic drugs are now approved after filing of an Abbreviated New Drug Application ("ANDA"), in which the manufacturer must show bioequivalency to a listed pioneer drug, but need not submit new safety studies. 21 U.S.C. § 355(j)(2)(A)(iv) and sentence at end of subsection (j)(2) (A). Generic drugs are required to have the same label as the listed drug. 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F. R. § 314.150(b)(10) (regulation allowing FDA to withdraw approval of an ANDA if labeling not consistent with listed drug).

> FN8. The Court notes that the key factual distinction between the present Paxil birth defect cases and *Colacicco* is that the FDA has never considered a warning with regard to birth defects. However, in the case at bar, only the generic manufacturer is left in the case, so the Court need not consider in this instance whether a failure to warn claim against a manufacturer of Paxil, a listed drug, is preempted.

Apotex further argues that while drug manufacturers of listed drugs have some ability to change or request a change to drug labeling by the FDA, a generic drug must continue to have the same label as the pioneer listed drug to which it is bioequivalent. Compare 21 C.F.R. 314.70(c)(6)(iii)(A) with 21 C.F.R. § 314.150(b)(10). Therefore, if state law regarding failure to warn is not preempted, it would be impossible for Apotex to meet both requirements.

Plaintiffs argue that the Hatch-Waxman Amendments act only to limit FDA actions toward generic manufacturers, but do not diminish Apotex's responsibilities to comply with state law. They argue that Apotex as a generic manufacturer could have sought an exception to the labeling requirements from the FDA to comply with state laws. Plaintiffs argue 21 C.F.R. § 314.150(b)(10) allows certain exceptions to the "same label" requirement. However, those exceptions relate only to whether a new patent was granted on the listed drug or whether a period of exclusivity is accorded to the listed drug. 21 C.F.R. § 314.150(b)(10)(i) and (ii).

Plaintiffs assert that Apotex had an obligation under both federal and state law to disclose all known risks and seek to update its labeling to protect the public safety, regardless of the FDA's limitations. They assert that Defendants could have complied with both state and federal law. They characterize their state law claims as "parallel claims" to the alleged violations of FDA regulations for the failure of Apotex to disclose known risks.

Finally, citing to case law from other Circuits, Plaintiffs assert that the Complaint alleges design defect claims that are not preempted. Even if federal labeling requirements preempt failure to warn claims, the FDA regulatory scheme does not shield manufacturers from liability for defects during the manufacturing or design process.

***7** Following the *Colacicco* opinion, only one district court has considered this exact question whether preemption does apply to claims against a generic manufacturer for failure to warn claims based upon the labeling ("labeling" includes inserts given to patients by physicians and/or pharmacists).[FN9] *Mensing v. Wyeth*, --- F.Supp.2d ----, 2008 WL 2444689 (D.Minn. June 17, 2008).[FN10] The Minnesota court concluded that a generic manufacturer has no legal duty to propose revised labeling to the FDA, and even if it does voluntarily propose such a change, approval of the change with regard to the generic product and the listed drug is left to the discretion of the FDA.2008 WL 2444689 at *8. Thus, the result of that request would "require speculation about what the FDA might have done."*Id.* Therefore, the Court concluded that imposing an affirmative state law duty to add safety information upon a generic manufacturer would directly conflict with the statutory scheme of the Hatch Waxman Act. *Id.*

> FN9. On July 18, 2008, Plaintiffs submitted a Notice of Supplemental Authority relying upon *Tucker v. SmithKline Beecham Corp.*, 2008 WL 2788505 (S.D.Ind.2008). In *Tucker*, the District Court reversed its earlier ruling dismissing the case on preemption grounds. This case involved a claim for failure to warn of increased suicidality upon ingestion of Paxil, a listed drug (i.e., not a generic drug).

> FN10. Another post-*Colacicco* decision concluded that state law claims were preempted against a generic manufacturer of an over-the-counter ("OTC") drug. *Gaeta v. Perrigo Pharmaceuticals Company*, --- F.Supp.2d ----, 2008 WL 2548813 (N.D.Cal. June 13, 2008). However, as in *Colacicco*, the *Gaeta* decision also mentioned that the FDA had once rejected a warning as to the ibuprofen drug at issue.
>
> A third decision involving similar facts as *Colacicco* also followed that decision. *Mason v. Smithkline Beecham Corp.*, 546 F.Supp.2d 618 (C.D.Ill.2008) (preemption of claims of failure to warn of suicidality

for Paxil).

This Court agrees with the analysis and conclusion of the decision in *Mensing* finding preemption of state law failure to warn claims against a generic manufacturer/distributor such as the Apotex Defendants. Because the FDA, pursuant to the FDCA statutory scheme as amended by the Hatch Waxman Act, requires generic drugs to have the same labeling as listed drugs, these federal laws preempt such a state law claim. Unlike a manufacturer of a listed drug, a generic manufacturer has a limited ability to even suggest a labeling change, subject solely to the discretion of the FDA to change the labeling for both the generic and the listed drug. Therefore, compliance with a state law duty to warn would conflict with the federal statutory scheme.

However, this preemption does not extend to manufacturing defect claims that arise separate and apart from a failure to warn claim. Given that the Complaint in this case appears to merge the theories of failure to warn and design/manufacturing defect under broader theories of negligence and strict liability, the Court will grant the present motion to dismiss, without prejudice to Plaintiffs filing an amended complaint separating out the failure to warn, design defect, and manufacturing defect claims.[FN11]

FN11. Plaintiffs may restate their failure to warn claims against the Apotex Defendants in the same document, which though they would be subject to dismissal pursuant to this Order, would allow a cleaner record for appellate purposes, and will allow the same claims to progress against SmithKline Beecham, who remains in this case.

IV. CONCLUSION

Accordingly, it is hereby **ORDERED** and **ADJUDGED** as follows:

1. Plaintiffs' Motion to Remand and for Attorneys Fees and Costs is hereby **DENIED** [DE 15];

2. Defendants Apotex Corp. and Apotex Inc.'s Motion to Dismiss [DE 8] is hereby **GRANTED in part** as to failure to warn claims, but **DENIED** as to design defect and manufacturing defect claims;

3. Plaintiffs shall file an Amended Complaint by August 29, 2008 pursuant to this Order;

4. The parties should submit a proposed scheduling order by August 29, 2008 regarding the parties' suggestions as to a trial date and pretrial deadlines.

DONE AND ORDERED.

S.D.Fla.,2008.
Valerio ex rel. Valerio v. SmithKline Beecham Corp.
Slip Copy, 2008 WL 3286976 (S.D.Fla.)

END OF DOCUMENT

EXHIBIT D

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List of Subjects in 21 CFR Part 179

Food additives, Food labeling, Food packaging, Radiation protection, Reporting and record keeping requirements, Signs and symbols.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 179 is amended as follows:

PART 179—IRRADIATION IN THE PRODUCTION, PROCESSING AND HANDLING OF FOOD

■ 1. The authority citation for 21 CFR part 179 continues to read as follows:

Authority: 21 U.S.C. 321, 342, 343, 348, 373, 374.

■ 2. Section 179.26 is amended in the table in paragraph (b) by adding a new item "12." under the headings "Use" and "Limitations" to read as follows:

§ 179.26 Ionizing radiation for the treatment of food.

* * * * *

(b) * * *

Use	Limitations
* * * * * * *	
12. For control of food-borne pathogens and extension of shelf-life in fresh iceberg lettuce and fresh spinach.	Not to exceed 4.0 kGy.

* * * * *

Dated: August 19, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E8–19573 Filed 8–21–08; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314, 601, and 814

[Docket No. FDA–2008–N–0032] (formerly Docket No. 2008N–0021)

RIN 0910–ZA32

Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations regarding changes to an approved new drug application (NDA), biologics license application (BLA), or medical device premarket approval application (PMA). This final rule provides that a supplemental application submitted under certain FDA regulations is appropriate to amend the labeling for an approved product to reflect newly acquired information and to add or strengthen a contraindication, warning, precaution, or adverse reaction if there is sufficient evidence of a causal association with the drug, biologic, or device, as defined in other FDA regulations and guidance documents.

DATES: This rule is effective September 22, 2008.

FOR FURTHER INFORMATION CONTACT:

For information regarding devices: Nicole Wolanski, Center for Devices and Radiological Health (HFZ–402), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 240–276–4010.

For information regarding biologics: Christopher Joneckis, Center for Biologics Evaluation and Research (HFM–1), Food and Drug Administration, 1401 Rockville Pike, Rockville MD 20852, 301–827–0373.

For information regarding drugs: Laurie Burke, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 6462, Silver Spring, MD 20933, 301–796–0900.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of January 16, 2008 (73 FR 2848), FDA proposed amending its regulations regarding changes to an NDA, BLA, or PMA to codify the agency's longstanding view concerning when a change to the labeling of an approved drug, biologic, or medical device may be made in advance of the agency's review and approval of such change (the January 2008 proposed rule). With respect to drugs, § 314.70(c)(6)(iii) (21 CFR 314.70(c)(6)(iii)) provides that certain labeling changes related to an approved drug may be implemented upon receipt by the agency of a supplemental new drug application (sNDA) that includes the change. The corresponding regulation for biological products, § 601.12(f)(2) (21 CFR 601.12(f)(2)), provides that products with certain labeling changes may be distributed before FDA approval. Similarly, with respect to devices, § 814.39(d) (21 CFR 814.39(d)) provides that certain labeling changes may be placed into effect upon submission of a PMA supplement, but prior to the sponsor's receipt of a written FDA order approving the supplement. The supplements described by §§ 314.70(c), 601.12(f)(2), and 814.39(d) are commonly referred to as "changes being effected supplements"

or "CBE supplements."[1] FDA proposed amending these provisions to affirm that a CBE supplement is appropriate to amend the labeling for an approved product only to reflect newly acquired information and to make it clear that a CBE supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug, biologic, or medical device. The phrase "sufficient evidence of a causal association" refers to the standards for drugs and biologics described in § 201.57(c)(6) (21 CFR 201.57(c)(6)) (for Warnings and Precautions—"reasonable evidence"), and in § 201.57(c)(7) (21 CFR 201.57(c)(7)) (for Adverse Reactions—"some basis to believe") and to the standard for devices in the Device Labeling Guidance, General Program Memorandum G91–1 (March 8, 1991) (*http://www.fda.gov/cdrh/g91-1.html*) ("reasonable evidence") for the level of evidence needed to support a causal association with these medical products.

As described in the January 2008 proposed rule, FDA believes that amending FDA's CBE regulations is consistent with the agency's role in protecting the public health. Before approving an NDA, BLA, or PMA, FDA undertakes a detailed review of the proposed labeling, allowing only information for which there is a scientific basis to be included in the FDA-approved labeling. Under the Federal Food, Drug, and Cosmetic Act (the act), the Public Health Service Act (the PHS Act), and FDA regulations, the agency makes approval decisions, including the approval of supplemental applications, based on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling. See, e.g., 21 U.S.C. 355(d); 42 U.S.C. 262; 21 U.S.C. 360e(d)(2). FDA's comprehensive scientific evaluation is embodied in the labeling for the product which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively. Expressly requiring that a CBE supplement reflect newly acquired information and be based on sufficient evidence of a causal association will help to ensure that scientifically accurate information appears in the approved labeling for such products.

[1] For devices, such supplements are also referred to as Special PMA Supplements. This document will use the term "CBE supplement."

II. Changes to the January 2008 Proposed Rule

FDA has made the following changes to the January 2008 proposed rule:

The definition of "newly acquired information" has been revised to clarify that data, whether derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) needs to be of a "different type or greater severity or frequency than previously included in submissions to FDA". The codified section of the January 2008 proposed rule suggested that this limitation applied only to data derived from reports of adverse events. Instead, it applies to data derived from new clinical studies, reports of adverse events, and new analyses of previously submitted data.

In addition, FDA has made one technical correction to the January 2008 proposed rule. The technical correction is in § 601.12, where an amendment was proposed adding paragraph (f)(5), containing the definition of "newly acquired information." In fact, the amendment should have proposed adding this definition to paragraph (f)(6) of § 601.12 rather than to paragraph (f)(5) of § 601.12.

III. Comments

FDA received approximately 20 comments to the January 2008 proposed rule. The comments were submitted by consumer advocacy groups, individuals, law firms, law professors, pharmaceutical companies, trade associations, and Members of Congress.

(Comment 1) Several comments stated that this proposed amendment would make it more difficult for sponsors to warn about new risks. Most of these comments were focused on the aspect of the rule that imposed a requirement that sponsors have a sufficient amount of causal evidence before a CBE should be used.

In addition, comments argued that FDA should distinguish between situations when sponsors are obligated to warn of a new risk, and situations when the sponsor is permitted to warn. For example, some comments stated that the requirement in § 201.57(c)(6) that there be some evidence of a causal relationship should apply to situations when a manufacturer must warn, but should not apply to when manufacturers may warn. These comments argue that public policy should not discourage sponsors from warning, even when the regulations do not require it.

Similarly, one comment argued that causation is not a binary issue (i.e., causation is either present or not). Rather, the causal relationship between a product and an adverse effect is often difficult to establish and may require large trials, often specifically designed to assess the risk. One comment argued that because of this difficulty, drug and device sponsors may delay warning and delay making labeling changes by asserting that the CBE regulation (if finalized as proposed) would not permit them to amend their labeling.

FDA does not agree that this rule will make it more difficult to provide appropriate warnings regarding hazards associated with medical products. This rule is intended to describe FDA's existing labeling standards and policies, but does not amend the standards under which sponsors must provide warnings regarding risks (§ 201.57(c)(6)). Nor is the rule intended to suggest that there is a mathematically precise distinction between whether there is, or is not, sufficient evidence of a causal relation between a drug and an adverse effect to support its inclusion in the labeling. The rule is, nevertheless, sufficiently clear and objective to allow sponsors to determine whether a medical product's labeling should be amended. If new safety information meets the requirements of § 201.57(c)(6), it is appropriate for inclusion in the labeling of a drug or biologic and a sponsor must update its labeling "as soon as" such information becomes available. That section states that causation need not have been "definitely established" for a warning to be required to appear in labeling, but rather that there need only be "reasonable" evidence of a causal association with the drug, a standard that could be met by a wide range of evidence. A CBE submission may be made when the evidence meets the standard set forth in this rule, even if that evidence would not also support a higher evidentiary standard, such as a finding that there is a "preponderance" of evidence that a product actually causes a particular kind of adverse event. A sponsor's submission or FDA's acceptance of a CBE supplement does not necessarily mean that a drug product actually has caused any particular adverse event or type of adverse event.

Through § 201.57 (and the predecessor regulation, now codified at § 201.80 (21 CFR 201.80)), the agency set uniform standards for drug labeling, seeking to ensure that scientifically sound information is provided in the labeling of the drug. There is no reason the standard for adding new information to labeling should be different from the

standard for the initial labeling. If new information about a drug comes to light, a sponsor must make a decision as to whether the requirements of § 201.57 are met, and whether to submit a CBE supplement or other type of supplemental application. Failure to update labeling as required could result in regulatory actions or criminal penalties. If there is doubt as to whether the standard of § 201.57(c)(6) has been met, a sponsor should confer with FDA. The agency has clarified by regulation and guidance the types of supplements that should be filed to satisfy a sponsor's obligations to change a drug's labeling, and sponsors can consult with FDA on that question as well. *See* 21 CFR 314.70; Guidance for Industry: Changes to an Approved NDA or ANDA (November 1999) (*http://www.fda.gov/cder/guidance/2766fnl.pdf*).

This rule does not undermine a sponsor's responsibility to maintain its label—rather, it clarifies FDA's longstanding practice of requiring that sponsors must have sufficient evidence that the standards are met (§ 201.57(c) and Device Labeling Guidance).

With respect to comments suggesting that § 201.57 sets the standard for when sponsors must warn, but that a lower standard should be used under § 314.70(c)(6) for when a sponsor may warn, FDA has previously stated and reiterates here that it "interprets the Act to establish both a 'floor' and a 'ceiling', such that additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading" (71 FR 3922 at 3935, January 24, 2006) (the 2006 Physician Labeling Rule). FDA, therefore, declines to set different standards for when a sponsor must warn, as opposed to when it may warn of a particular risk or adverse event.

(Comment 2) Several comments stated that the rule would conflict with the intent of Congress. FDA in no way believes that this rule conflicts with Congressional intent. Another, comment stated that Congress did not intend for the act to preempt State law because there is no express preemption provision with respect to drugs. Several comments referred to the recently enacted Food and Drug Administration Amendments Act of 2007 (FDAAA) in support of this position. These comments suggest that for FDA to change the circumstances when sponsors could update their labeling by a CBE would conflict with congressional intent. FDAAA provided additional authority for FDA to require sponsors to make safety related changes to their labeling. The statute also included a rule of construction as part of a paragraph providing new authority to the Secretary to require labeling changes for drug products: "This paragraph shall not be construed to affect the responsibility of the responsible person or the holder of the approved application under section 505(j) to maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations)." (Section 505(o)(4)(I) of the act (21 U.S.C. 355(o)(4)(I))).

FDA does not believe that the absence of an express preemption provision with respect to drugs affects the application of the doctrine of implied preemption. Furthermore, FDA does not agree that the rule of construction affects FDA's ability to finalize the January 2008 proposed rule for several, independent reasons.[2] The January 2008 proposed regulation is consistent with the rule of construction. First, the rule of construction, by its terms, contemplates amendments to applicable regulations by its reference to "successor regulations" governing a sponsor's obligation to change product labeling. Congress, therefore, expressly acknowledged that FDA's regulations are not static and may be subsequently amended by the agency, as FDA is doing here. Second, the rule of construction operates to preserve Federal labeling obligations only in the face of an argument that "this paragraph"—21 U.S.C. 355(o)(4), the new statutory provision permitting the Secretary of Health and Human Services (the Secretary) to impose labeling changes after meeting certain procedural requirements—"affects" those responsibilities. Third, the rule of construction refers to, and therefore preserves only a sponsor's Federal-law (as opposed to State-law) "responsibility[ies] * * * to maintain its label." As was noted in the U.S. Government's amicus brief at the merits stage in *Wyeth* v. *Levine*, No. 06–1249 (June 2008) (*http://www.justice.gov/osg/briefs/2007/3mer/1ami/2006-1249.mer.ami.pdf*), the rule of construction "simply means that the relevant amendments do not affect obligations under other *federal* laws. It does not manifest any intent to depart from the application of ordinary principles governing the preemption of conflicting *state* laws. * * * [T]he text of the rule of construction that Congress actually enacted, which is limited to the effect of Section 901, itself preserves *complementary federal* requirements without evincing any intent to protect *conflicting state* laws." *Id.* at 32 (emphases in original).

(FDA has verified the Web site addresses in this document, but FDA is not responsible for subsequent changes after this document publishes in the **Federal Register**).

In other words, the rule of construction makes it clear that a sponsor cannot contend that, because the Secretary has the power to order new labeling changes, the sponsor no longer has an obligation to monitor post-marketing experiences and maintain its labeling under applicable Federal regulations. Indeed, it can maintain its labeling by using all existing tools, including through prior approval supplements, CBE-30 day supplements (§§ 314.70(c), 601.12(c) and 814.39(e)), and CBE supplements, along with other changes that may be reported in an annual report. Under both the rule of construction and this final rule, a sponsor still must update its labeling under Federal law "to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug" (§ 201.57(c)(6)), and add other risk information as required by the regulations (§ 201.57(c)).

If FDA were to interpret section 505(o)(4) of the act as eliminating the ability or obligation under Federal law of a sponsor to "maintain" its label, this would conflict with the rule of construction. But this final rule does not take away a sponsor's obligation to maintain its labeling under Federal law under appropriate circumstances. FDA is amending the text of the rules at issue here not because of the new powers in section 505(o)(4) of the act, but to clarify a sponsor's responsibilities and to make the text of the regulations match FDA's practice regarding CBE labeling changes, which predate FDAAA. Manufacturers continue to have a responsibility under Federal law, including the amended regulations under this rulemaking, to maintain their labeling and update the labeling with new safety information.

(Comment 3) One comment asserted that this rule could undermine consumer confidence in medical products and FDA. Consumer confidence in medical products and in FDA itself is critically important. This amendment is intended to clarify FDA's existing policies and is intended to ensure that scientifically valid and appropriately worded warnings will be provided in the approved labeling for medical products, and to prevent overwarning, which may deter

[2] FDA notes that the rule of construction in 21 U.S.C. 355(o)(4) on its face does not relate to medical devices.

appropriate use of medical products, or overshadow more important warnings. Accordingly, FDA does not agree that the rule will undermine confidence in medical products or the agency.

(Comment 4) One comment stated that the January 2008 proposed rule's reference to "newly acquired information" might undermine warnings in situations where a sponsor warns about a particular risk, but then later information demonstrates that the warning was insufficient.

FDA believes that the final rule addresses this concern. First, if later data or analyses demonstrate that prior warnings were insufficient, such data would clearly qualify as newly acquired information under the rule. Indeed, the rule expressly provides that new analyses of previously submitted information are considered new information that could be submitted by a CBE supplement (provided that other requirements for a CBE supplement are met). Therefore, if a sponsor determined that existing warnings were insufficient based on newly acquired information such as a new analysis of previously submitted data, the sponsor could still submit a CBE based on its new analysis of the previous data, provided the other requirements of the rule are met. Moreover, FDA now has new tools to address this situation, including its authority to require labeling changes under section 505(o) of the act.

(Comment 5) Several comments asserted that sponsors, not FDA, have the most information about their products and should have authority to revise their labeling as soon as new information comes to light.

Sponsors are still required to act promptly to add risk information to labeling (§ 201.57(c)(6)). This rule describes the standard for one type of change to the labeling. It is intended to clarify the circumstances in which sponsors are required to update labeling, not to undermine or remove a sponsor's obligation to modify labeling to reflect appropriate new information. Under FDA's regulations and this final rule, sponsors are required to warn as soon as appropriate new information comes to light (§ 201.57(c)(6)).

(Comment 6) Several comments stated that FDA did not have sufficient resources to review all potential warnings before labeling may be updated. As stated in the January 2008 proposed rule, FDA does not consider this amendment to substantively change the standards for submission of CBE or prior review supplements. The agency does not expect that it will increase the number of prior approval supplements or otherwise increase agency workloads.

(Comment 7) One comment requested that FDA clarify the relationship between the January 2008 proposed rule and statements made by FDA in the preamble to the 2006 Physician Labeling Rule (71 FR 3922). The comment inquired whether these changes "supersede" certain statements in the preamble to the 2006 Physician Labeling Rule. The agency believes that these amendments are consistent with prior statements by FDA, including those in the 2006 Physician Labeling Rule. The preamble to the 2006 Physician Labeling Rule set forth a number of principles regarding FDA's regulation of drug labeling. See, e.g. 71 FR 3922 at 3935 ("FDA interprets the act to establish both a 'floor' and a 'ceiling,' such that additional disclosures of risk information can expose a manufacturer to liability under the act" * * *); ibid. ("State-law attempts to impose additional warnings can lead to labeling that does not accurately portray a product's risks, thereby potentially discouraging safe and effective use of approved products * * *"). That preamble also set forth some non-exclusive examples of instances of preemption. Id. at 3935–3936 (stating that "at least" the enumerated cases are preempted). In a proposed rule that published in the Federal Register of May 29, 2008 (73 FR 30831 at 30861), FDA reiterated its support for the general principles underlying preemption set forth in the 2006 Physician Labeling Rule. In briefs recently filed in the Supreme Court of the United States and in testimony before Congress, FDA has also stated a more generally applicable rule that is consistent with the examples of preempted cases and the principles set forth in the preamble to the 2006 Physician Labeling Rule that: (1) The labeling requirements are not a mere minimum safety standard, but rather strike a balance between risks and benefits, and (2) FDA's regulations permit changes in labeling without prior approval only in narrow circumstances. Specifically, FDA has explained that State law claims that "challenge labeling that FDA approved after being informed of the relevant risk" are preempted. Brief of the United States as Amicus Curiae Supporting Petitioner, *Wyeth* v. *Levine*, No. 06–1249; Testimony of Deputy FDA Commissioner Randall Lutter before The House Committee on Oversight and Government Reform 5 (2008) *http://oversight.house.gov/documents/20080514142253.pdf* ("* * * State law claims are preempted if they challenge a design or labeling that FDA approved, after being informed of the relevant health risk * * *"). FDA reiterates and reaffirms here the positions set forth in those documents. FDA further notes that FDA there explained the interplay between this CBE regulation and preemption. FDA believes that this explanation sufficiently describes the relationship between this CBE regulation and the 2006 Physician Labeling Rule preamble.

(Comment 8) One comment requested that FDA make it clear that information previously known to the manufacturer, but not submitted to FDA, can be eligible for inclusion in a CBE amendment.

The term "newly acquired information" is defined in the final rule as "information not previously submitted to FDA * * *." Accordingly, if information was previously known to the manufacturer, but not submitted to FDA, it would be "newly acquired information" that may qualify for inclusion in a CBE supplement (provided other requirements for a CBE supplement have been met).

(Comment 9) Several comments requested that FDA clarify the effect of this amendment on State tort liability and preemption, and one comment stated that this rule lacked a sufficient statement of irreconcilable conflict to justify the agency's assertion of implied preemption of "all [S]tate law". This rule does not preempt all State tort law and, furthermore, an "irreconcilable conflict" (i.e., an impossibility of compliance with both Federal and State law) is not the only basis for preemption of State law. Under implied preemption principles, if a State law frustrates Federal objectives, the State law is preempted. As a result, FDA's views on preemption, as explained elsewhere in this preamble, are amply justified by well-established principles of preemption. See *Geier* v. *American Honda Co.*, 529 U.S. 861 (2000); *English* v. *General Electric Co.*, 496 U.S. 72, 79 (1990); *Florida Lime & Avocado Growers, Inc.*, 373 U.S. 132, 142–43 (1963); *Hines* v. *Davidowitz*, 312 U.S. 52, 67 (1941). Moreover, liability imposed under State tort law constitutes a State "requirement" within the meaning of 21 U.S.C. 360k(a). See *Reigel* v. *Medtronic*, 128 S.Ct. 999, 1008–09 (2008). For further discussion of the scope of preemption, see the response to comment 7 of this document and section VIII. Federalism of this document.

(Comment 10) One comment requested that FDA develop an alternative mechanism to address proposed labeling changes. FDA believes that its regulations (as modified

in this final rule) provide appropriate and adequate regulatory pathways for updating and modifying labeling of drugs, biological products, and medical devices. See § 314.70(c) (for drugs), § 601.12(f)(2) (for biological products) and § 814.39(d) (for medical devices).

(Comment 11) One comment requested that FDA clarify the degree of certainty that is required for demonstrating causation under FDA's regulations. FDA does not believe that additional clarification of its labeling rules is necessary. The regulations set forth in § 201.57 provide relevant standards for when information is appropriate for inclusion in labeling, including causation standards. FDA believes that standard is sufficiently clear and objective.

(Comment 12) One comment noted that the preamble to the January 2008 proposed rule stated that "FDA intends to consider information 'newly acquired' if it consists of data, analyses, or other information not previously submitted to the agency, or *submitted within a reasonable time period prior to the CBE supplement* * * *." (73 FR 2848 at 2850) (emphasis added). The comment requested that FDA clarify the temporal relationship between the submission of new information to FDA and a subsequent CBE supplement. FDA agrees that this issue should be clarified here so as to provide greater guidance to sponsors in determining their regulatory obligations. Newly acquired information includes information not previously submitted to FDA. If a sponsor submits data or analysis to FDA as part of a discussion of the kind of labeling change that would be appropriate and decides as a result of that discussion to prepare and submit a CBE supplement, then the supporting data or analysis will not be considered "previously submitted to FDA"—even if it was not first submitted on the same day as the CBE supplement. This allows for a labeling change when a sponsor submits data or analysis to FDA before the sponsor has completed its CBE supplement, and is also designed so as not to deter the sponsor from submitting the information for fear that such a submission would preclude the sponsor from making a CBE change. This clarification is designed to address the situation where a sponsor submits data or analyses to FDA as part of the process of determining what labeling change is appropriate, and then diligently and promptly prepares a CBE supplement.

Moreover, FDA also notes that the definition of "newly acquired information" includes "new analyses" of previously submitted information. If a sponsor submits information to FDA, then later conducts a new analysis that demonstrates that labeling should be revised to account for that information, a CBE would be appropriate. For example, if the sponsor submits adverse event information to FDA, and then later conducts a new analysis of data showing risks of a different type or of greater severity or frequency than did reports previously submitted to FDA, the sponsor meets the requirement for "newly acquired information".

(Comment 13) One comment requested that FDA clarify the relationship between the CBE regulations and risk evaluation and mitigation strategies (REMS) for drugs and biological products.

Under the new authority provided in FDAAA, FDA may require the submission of a proposed REMS if FDA believes that such a strategy is necessary to ensure that the benefits of the drug outweigh its risks. A REMS must be approved by FDA (21 U.S.C. 355–1(h)), as must proposed modifications to a REMS (21 U.S.C. 355–1(g)). Accordingly, if the labeling for a drug describes an element of an approved REMS, the sponsor must receive prior approval of any labeling changes that would necessitate a change to the sponsor's REMS. For example, if a REMS included elements to assure safe use under section 505–1(f) of the act, some of those elements might be described in the approved labeling for the drug or biologic. If the sponsor became aware of newly acquired safety information that would otherwise be appropriate for a CBE, but would require the sponsor to modify an element to assure safe use that is required under a REMS, the sponsor would need to receive prior approval of the labeling change. However, if the newly acquired information is related to the concern leading to a REMS but the proposed change to labeling could be made without requiring a modification of the REMS, the approved labeling for the product could be strengthened without prior approval. For example, if a REMS was imposed requiring periodic monitoring of liver enzymes to ensure the risk of liver toxicity for a drug was outweighed by the benefits of the drug, strengthening warnings related to that risk may be made by a CBE supplement (provided that other requirements for a CBE supplement are met and that the change can be made without modifying the REMS).

(Comment 14) One comment requested that FDA clarify that any change to the Highlights section of the labeling of a drug or biologic must be made by a prior approval supplement.

The agency agrees that this issue should be clarified, but does not agree that changes to Highlights can never be accomplished by a CBE supplement. Under existing regulations, changes to the Highlights are classified as a "major change," requiring a prior approval supplement (§ 314.70(b)(2)(v)(C)). Accordingly, in most cases, changes to Highlights will require a prior approval supplement. However, in the preamble to the January 2008 proposed rule, we noted that FDA could waive this limitation under § 314.90 or request that a sponsor make a change to Highlights under § 314.70(c)(6)(iii)(E) or § 601.12(f)(2)(E). These provisions authorize FDA to waive the Highlights limitation or otherwise ask the sponsor to submit a CBE supplement in appropriate circumstances.

(Comment 15) One comment requested that FDA clarify that sponsors may not use the CBE process to submit labeling changes for drugs or biological products under section 505(o) of the act.

FDA disagrees with this comment. Under section 505(o) of the act, FDA must notify the sponsor if the agency becomes aware of new safety information that should be included in the labeling for a particular drug or biologic. Following that notification, the sponsor must submit a "supplement" proposing changes to the labeling or submit a statement explaining the reasons why the sponsor believes the labeling change is not warranted. Nothing in section 505(o) limits this "supplement" to a prior approval supplement. In fact, to effect the change most rapidly, FDA may request that the sponsor file a CBE supplement under these circumstances.

(Comment 16) One comment requested that FDA provide a comprehensive, written response to every CBE supplement submitted to the agency by a sponsor, describing FDA's grounds for approval, disapproval, or, as the case may be, request for modification to the submitted CBE supplement. FDA disagrees with this comment. The comment failed to provide a compelling justification for this proposal.

(Comment 17) One comment asserted that if FDA finalizes this rule, it will create a disincentive for sponsors to conduct additional trials of their products because the sponsors would have to provide additional warnings if causation is shown. Under current regulations, sponsors must warn about risks of approved products if the requirements for updating labeling are triggered. This rule does not change those standards. FDA therefore does not believe that it will change the incentives

for sponsors to conduct new clinical trials.

(Comment 18) One comment stated that the rule would unjustifiably impose an added regulatory burden. FDA disagrees with this comment, as this rule does not add to the existing regulatory burden. Rather, as previously stated, the rule simply affirms that a CBE supplement is appropriate to amend the labeling for an approved product only to reflect newly acquired information and makes it clear that a CBE supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug, biologic, or medical device. For further discussion of the regulatory burden, see sections V. Analysis of Impacts and VI. Paperwork Reduction Act of this document.

IV. Legal Authority

As explained in the January 2008 proposed rule, FDA's legal authority to modify §§ 314.70, 601.12, and 814.39 arises from the same authority under which FDA initially issued these regulations. The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 *et seq.*) and the Public Health Service Act (42 U.S.C. 201 *et seq.*) provide FDA with authority over the labeling for drugs, biological products, and medical devices, and authorize the agency to enact regulations to facilitate FDA's review and approval of applications regarding the labeling for such products.

Section 502 of the act (21 U.S.C. 352) provides that a drug, biologic,[3] or medical device will be considered misbranded if, among other things, the labeling for the product is false or misleading in any particular (21 U.S.C. 352(a)). Under section 502(f) of the act, a product is misbranded unless its labeling bears adequate directions for use, including adequate warnings against, among other things, unsafe dosage or methods or duration of administration or application. Moreover, under section 502(j) of the act, a product is misbranded if it is dangerous to health when used in the manner prescribed, recommended, or suggested in its labeling.

In addition to the misbranding provisions, the premarket approval provisions of the act authorize FDA to require that product labeling provide adequate information to permit safe and effective use of the product. Under section 505 of the act (21 U.S.C. 355), FDA will approve an NDA only if the drug is shown to be both safe and effective for its intended use under the conditions set forth in the drug's labeling. Similarly, under section 515(d)(2) of the act (21 U.S.C. 360e(d)(2)), FDA must assess whether to approve a PMA according to the "conditions of use prescribed, recommended, or suggested in the proposed labeling" of the device. Section 701(a) of the act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the act.

Section 351 of the PHS Act (42 U.S.C. 262) provides additional legal authority for the agency to regulate the labeling of biological products. Licenses for biological products are to be issued only upon a showing that the biological product is safe, pure, and potent (42 U.S.C. 262(a)). Section 351(b) of the PHS Act (42 U.S.C. 262(b)) prohibits any person from falsely labeling any package or container of a biological product. FDA's regulations in part 201 apply to all prescription drug products, including biological products.

V. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is not a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because these amendments to existing regulations are intended only to codify the agency's interpretation of current policy, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $127 million, using the most current (2006) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

The objective of the final rule is to make explicit the agency's view of when a change to the labeling of an approved drug, biologic, or medical device may be made in advance of the agency's review of the change. More specifically, the purpose of the final rule is to clarify that a CBE supplement is appropriate to amend the labeling for an approved product only to reflect newly acquired information, and to clarify that a CBE supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is reasonable evidence of a causal association with the approved drug, biologic, or medical device. FDA does not consider this to be a substantive policy change, and it does not alter the agency's current practices with respect to accepting or rejecting labeling changes proposed by a CBE supplement.

Because this final rule does not establish any new regulatory or recordkeeping requirements, the agency does not expect that there will be any associated compliance costs. The final rule simply clarifies the agency's interpretation of when sponsors are allowed to add information regarding the risks associated with a product to the labeling without prior approval from FDA. It is expected that these clarifications will promote more effective and safe use of approved drug, biologic, and medical device products. The agency believes that any potential impacts of these amendments to existing regulations will be minimal because this action does not represent a substantive change from current policy. We did not receive any comments on the January 2008 proposed rule that would cause us to reconsider these determinations.

VI. Paperwork Reduction Act of 1995

This final rule refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 35013520). The collections of information in 21 CFR part 314 have been approved under OMB Control No. 0910–0001 (expires May 31, 2011); 21 CFR part 601 have been approved under OMB Control No. 0910–0338 (expires June 30, 2010); and 21 CFR part 814 have been approved under OMB Control No. 0910–0231 (expires November 30, 2010). Therefore,

[3] Although the language of section 502 of the act refers only to drugs and devices, it is also applicable to biologics. (See 42 U.S.C. 262(j)).

clearance by OMB under the PRA is not required.

VII. Environmental Impact

The agency has determined under 21 CFR 25.31(a) and 25.34(e) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires agencies to "construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute." Like any Federal requirement, if a State law requirement makes compliance with both Federal law and State law impossible, or would frustrate Federal objectives, the State requirement would be preempted. See *Geier* v. *American Honda Co.*, 529 U.S. 861 (2000); *English* v. *General Electric Co.*, 496 U.S. 72, 79 (1990); *Florida Lime & Avocado Growers, Inc.*, 373 U.S. 132, 142–43 (1963); *Hines* v. *Davidowitz*, 312 U.S. 52, 67 (1941). Moreover, if a State requirement constitutes a requirement that is different from, or in addition to, a Federal requirement applicable to a medical device, and which relates to the safety or effectiveness of the device, the State law requirement is preempted. See 21 U.S.C. 360k(a), *Reigel* v. *Medtronic*, 128 S.Ct. 999 (2008). In addition to the discussion above in response to comment 7 of this document, FDA notes that, at least when a sponsor did not meet the standard to change its labeling through a CBE supplement under this rule to include the warning a plaintiff alleges should have been added to labeling, State law liability that is premised on a failure to warn is preempted.

FDA has provided the States with an opportunity to comment on the January 2008 proposed rule. Specifically, following publication of the January 2008 proposed rule in the Federal Register, FDA issued a "Dear Colleague" letter on January 17, 2008. The purpose of this letter was to alert officials in various organizations within the 50 States about the rulemaking, including officials with State pharmacy boards, State medical boards, health commissioners, and drug program directors. The letter briefly explained what the rulemaking would do when it became final and it encouraged the officials to review the January 2008 proposed rule and provide FDA with any comments they may have concerning the impact this rule may have on the following: (1) On the States, (2) on the relationship between the national government and the States, or (3) on the distribution of power and responsibilities among the various levels of government. FDA received one comment that appears to be in response to this "Dear Colleague" letter. This comment is addressed in the final rule.

List of Subjects

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

21 CFR Part 814

Administrative practice and procedure, Confidential business information, Medical devices, Medical research, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 314, 601, and 814 are amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

■ 1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 356a, 356b, 356c, 371, 374, 379e.

■ 2. Section 314.3 is amended in paragraph (b) by alphabetically adding the definition for "newly acquired information" to read as follows:

§ 314.3 Definitions.

* * * * *

(b) * * *

Newly acquired information means data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

* * * * *

■ 3. Section 314.70 is amended by revising paragraphs (c)(6)(iii) introductory text and (c)(6)(iii)(A) to read as follows:

§ 314.70 Supplements and other changes to an approved application.

* * * * *

(c) * * *

(6) * * *

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

* * * * *

PART 601—LICENSING

■ 4. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

■ 5. Section 601.12 is amended by revising paragraphs (f)(2)(i) introductory text and (f)(2)(i)(A), and by adding paragraph (f)(6) to read as follows:

§ 601.12 Changes to an approved application.

* * * * *

(f) * * *

(2) *Labeling changes requiring supplement submission—product with a labeling change that may be distributed before FDA approval.* (i) An applicant shall submit, at the time such change is made, a supplement for any change in the package insert, package label, or container label to reflect newly acquired information, except for changes to the package insert required in § 201.57(a) of this chapter (which must be made under paragraph (f)(1) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

* * * * *

(6) For purposes of paragraph (f)(2) of this section, information will be considered newly acquired if it consists of data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

* * * * *

PART 814—PREMARKET APPROVAL OF MEDICAL DEVICES

■ 6. The authority citation for 21 CFR part 814 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 353, 360, 360c–360j, 371, 372, 373, 374, 375, 379, 379e, 381.

■ 7. Section 814.3 is amended by adding paragraph (o) to read as follows:

§ 814.3 Definitions.

* * * * *

(o) *Newly acquired information* means data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

■ 8. Section 814.39 is amended by revising paragraphs (d)(1) introductory text and (d)(2)(i) to read as follows:

§ 814.39 PMA supplements.

* * * * *

(d)(1) After FDA approves a PMA, any change described in paragraph (d)(2) of this section to reflect newly acquired information that enhances the safety of the device or the safety in the use of the device may be placed into effect by the applicant prior to the receipt under § 814.17 of a written FDA order approving the PMA supplement provided that:

* * * * *

(2) * * *

(i) Labeling changes that add or strengthen a contraindication, warning, precaution, or information about an adverse reaction for which there is reasonable evidence of a causal association.

* * * * *

Dated: August 19, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E8–19572 Filed 8–21–08; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HOMELAND SECURITY

Coast Guard

33 CFR Part 100

[Docket No. USCG–2008–0424]

Special Local Regulation; U.S. Nationals Waterski Racing Championship; Mission Bay, San Diego, CA

AGENCY: Coast Guard, DHS.

ACTION: Notice of enforcement of regulation.

SUMMARY: The Coast Guard will enforce the U.S. Nationals Waterski Racing Championship special local regulation on Mission Bay from 8 a.m. on October 10, 2008 through 5 p.m. on October 12, 2008. This action is necessary to provide for the safety of the participants, crew, spectators, participating vessels, and other vessels and users of the waterway. During the enforcement period, no person or vessel may enter the special local regulation without permission of the Captain of the Port.

DATES: The regulations in 33 CFR 100.1101 will be enforced from 8 a.m. on October 10, 2008 through 5 p.m. on October 12, 2008.

FOR FURTHER INFORMATION CONTACT: Petty Officer Kristen Beer, USCG, Waterways Management, U.S. Coast Guard Sector San Diego at (619) 278–7233.

SUPPLEMENTARY INFORMATION: The Coast Guard will enforce the special local regulation for the U.S. Nationals Waterski Racing Championship in 33 CFR 100.1101 on October 10, 2008, from 8 a.m. to 7 p.m., October 11, 2008, from 8 a.m. to 7 p.m., and October 12, 2008, from 8 a.m. to 7 p.m.

Under the provisions of 33 CFR 100.1101, a vessel may not enter the regulated area, unless it receives permission from the COTP. Spectator vessels may safely transit outside the regulated area but may not anchor, block, loiter in, or impede the transit of participants or official patrol vessels. The Coast Guard may be assisted by other Federal, State, or local law enforcement agencies in enforcing this regulation.

This notice is issued under authority of 33 CFR 100.1101(a) and 5 U.S.C. 552(a). In addition to this notice in the **Federal Register**, the Coast Guard will provide the maritime community with extensive advance notification of this enforcement period via the Local Notice to Mariners, marine information broadcasts, local radio stations and area newspapers. If the COTP or his designated representative determines that the regulated area need not be enforced for the full duration stated in this notice, he or she may use a Broadcast Notice to Mariners to grant general permission to enter the regulated area.

Dated: August 8, 2008.

T.H. Farris,

Captain, U.S. Coast Guard, Captain of the Port Sector San Diego.

[FR Doc. E8–19532 Filed 8–21–08; 8:45 am]

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DEPARTMENT OF HOMELAND SECURITY

Coast Guard

33 CFR Part 165

[Docket Number USCG–2008–0769]

Oregon Symphony Celebration Fireworks Display, Portland, OR

AGENCY: Coast Guard, DHS.

ACTION: Notice of enforcement of regulation.

SUMMARY: The Coast Guard will enforce the "Oregon Symphony Celebration Fireworks Display safety zone on the Willamette River"; from 8:30 p.m. through 11:30 p.m. on August 28, 2008. This action is necessary to provide a safe display for the public and to keep them clear of the fall out area of the fireworks. During the enforcement period, no person or vessel may enter the safety zone without permission of the Captain of the Port Portland or his designated representative.

DATES: The regulations in 33 CFR 165.1315(a)(7) will be enforced from 8:30 p.m. through 11:30 p.m. on August 28, 2008.

FOR FURTHER INFORMATION CONTACT: BM2 Joshua Lehner, Sector Portland Waterways Management at (503) 247–4015.

SUPPLEMENTARY INFORMATION: The Coast Guard will enforce the safety zone for the Oregon Symphony Celebration Fireworks Display in 33 CFR 165.1315(a)(7) on August 28, 2008 from 8:30 p.m. to 11:30 p.m.